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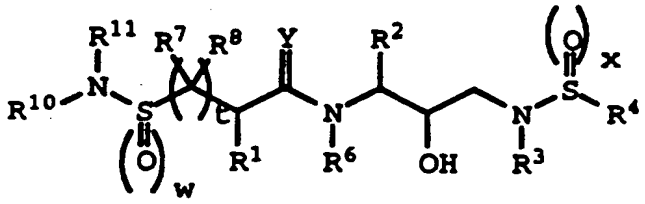


(I)

(57) Abstract

Bis-sulfonamido hydroxyethylamino compounds are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease. The present invention relates to retroviral protease inhibiting compounds of formula (I) or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein the variables are as defined herein.

BIS-SULFONAMIDE HYDROXYETHYLAMINO RETROVIRAL PROTEASE INHIBITORS

RELATED APPLICATION

This application is a continuation-in-part application of U.S. Patent Application Serial No. 08/376,337, filed January 20, 1995.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to bis-sulfonamide-containing hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene transcription products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virons. For example, it has been shown that

G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. EP 468 641 discloses renin inhibitors and intermediates for the preparation of the inhibitors, which include sulfonamide-containing hydroxyethylamine compounds, such as 3-(t-butoxycarbonyl)amino-cyclohexyl-1-(phenylsulfonyl)amino-2(5)-butanol. G.B. 2,200,115 also discloses sulfamoyl-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfonamide-containing hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to a method of inhibiting retroviral proteases, to processes for preparing the compounds and to intermediates useful in such processes. The subject compounds are characterized as bis-sulfonamide-containing hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retroviral protease inhibiting compound of the formula:

alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide derivatives thereof;

R^4 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heteroaryl, heterocycloalkyl, aryl, aralkyl, heteroaralkyl, thioalkyl, alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide derivatives thereof, or aminoalkyl or N-mono- or N,N-disubstituted aminoalkyl radicals, wherein said substituents are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocyclo, heterocycloalkyl, thioalkyl, alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide derivatives thereof;

R^6 represents hydrogen or alkyl radicals;

each R^7 independently represents radicals as defined for R^1; or R^7 together with R^1 and the carbon atoms to which R^1 and R^7 are attached, represent cycloalkyl or heterocyclo radicals;

each R^8 independently represents hydrogen or alkyl radicals;

R^{10} and R^{11} each independently represent radicals as defined for R^3; or R^{10} and R^{11} together with the nitrogen to which they are attached represent heterocyclo or heteroaryl radicals;

x and w each represent 0, 1 or 2;

t represents 0-6; and

Y represents O, S or NH.

heteroaralkyl, heterocyclo, heterocycloalkyl, thioalkyl, alkylthioalky radicals or the corresponding sulfone or sulfoxide derivatives thereof;

R^4 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heteroaryl, heterocycloalkyl, aryl, aralkyl; heteroaralkyl, thioalkyl, alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide N,N-derivatives thereof, aminoalkyl or N-mono- or disubstituted aminoalkyl radicals, wherein said substituents are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocyclo, heterocycloalkyl, thioalkyl, alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide derivatives thereof;

R^6 represents hydrogen or alkyl radicals;

each R^7 independently represents radicals as defined for R^1; or R^7 together with R^1 and the carbon atoms to which R^1 and R^7 are attached, represent a cycloalkyl or heterocyclo radical;

each R^8 independently represents hydrogen or alkyl radicals;

R^{10} and R^{11} each independently represent radicals as defined for R^3; or R^{10} and R^{11} together with the nitrogen to which they are attached represent heterocyclo or heteroaryl radicals;

t represents 0-4; and

Y represents O, S or NH.

each R^8 independently represents hydrogen or alkyl radicals;

R^{10} and R^{11} each independently represent hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heteroaryl, heterocycloalkyl, aryl, aralkyl, heteroaralkyl, thioalkyl, alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide derivatives thereof, aminoalkyl or N-mono- or N,N-disubstituted aminoalkyl radicals, wherein said substituents are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocyclo, heterocycloalkyl thioalkyl, alkylthioalky radicals or the corresponding sulfone or sulfoxide derivatives thereof; or R^{10} and R^{11} together with the nitrogen to which they are attached represent heterocyclo or heteroaryl radicals;

t represents 0-2; and

Y represents O or S.

Of highest interest are compounds within Formula II wherein

R^1 represents hydrogen, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, methyl, ethyl, isopropyl, iso-butyl, sec-butyl, tert-butyl, propenyl or propargyl radicals, or an amino acid side chain of asparagine, S-methyl cysteine, isoleucine, allo-isoleucine, alanine, tert-leucine or valine;

R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl, fluorobenzyl, naphthylmethyl, cyclohexylmethyl, phenylthiomethyl or naphthylthiomethyl radicals;

methylpiperazinyl, N-ethylpiperazinyl, N-benzylpiperazinyl, N-(pyridylmethyl)piperazinyl, N-(tetrahydrothienylmethyl) piperazinyl, N-(thiazolylmethyl)piperazinyl, N-(furylmethyl)piperazinyl, N-(benzoxazolylmethyl) piperazinyl, N-(piperidinylethyl)piperazinyl, N-(morpholinoethyl)piperazinyl and the like;

t represents 0 or 1; and

Y represents O or S.

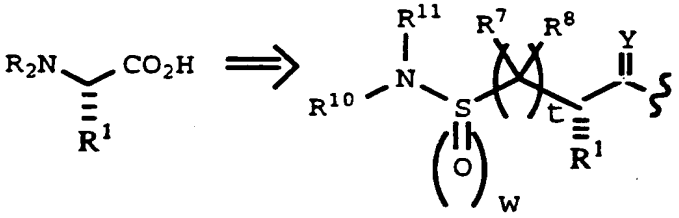
The absolute stereochemistry of the carbon atom of -CH(OH)- group is preferably (R). The absolute stereochemistry of the carbon atom of -CH(R^1)- group is preferably (S). The absolute stereochemistry of the carbon atom of-CH(R^2)- groups is preferably (S).

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing preferably from 1 to 10 carbon atoms, more preferably from 1 to 8 carbon atoms, most preferably 1-5 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term "thioalkyl" means an alkyl radical as defined above which is substituted by at least one -SH group. "Alkylthioalkyl" and "arylthioalkyl" means an alkyl radical as defined above which is substituted by at least one alkyl-S and aryl-S-, respectively, where alkyl and aryl are as defined herein. Examples of thioalkyl, alkylthioalkyl and arylthioalkyl are $-CH_2SCH_2CH_3$, $-CH_2CH_2SH$, $-C(CH_3)_2SH$, $-C(CH_3)_2SCH_3$, $-(CH_2)_2SCH_3$, $-CH_2$S-phenyl and the like. The corresponding sulfoxide and sulfone of such thioalkyls are $-CH_2S(O)CH_2CH_3$, $-C(CH_3)_2S(O)CH_3$, $-C(CH_3)_2S(O)CH_3$, $-CH_2S(O)_2CH_2CH_3$, $-C(CH_3)_2S(O)_2CH_3$, $-CH_2S(O)$phenyl, $-CH_2-$

cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylbutyl and the like. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which is optionally substituted with one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocyclo, alkanoylamino, amido, amidino, alkoxycarbonylamino, N-alkylamidino, alkylamino, dialkylamino, N-alkylamido, N,N-dialkylamido, aralkoxycarbonylamino, alkylthio, alkylsulfinyl, alkylsulfonyl and the like. Examples of aryl radicals are phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl, piperazinylphenyl and the like. The terms "aralkyl" and "aralkoxy", alone or in combination, means an alkyl or alkoxy radical as defined above in which at least one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, benzyloxy, 2-phenylethyl, dibenzylmethyl, hydroxyphenylmethyl, methylphenylmethyl, diphenylmethyl, diphenylmethoxy, 4-methoxyphenylmethoxy and the like. The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which the term "aralkyl" has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid,

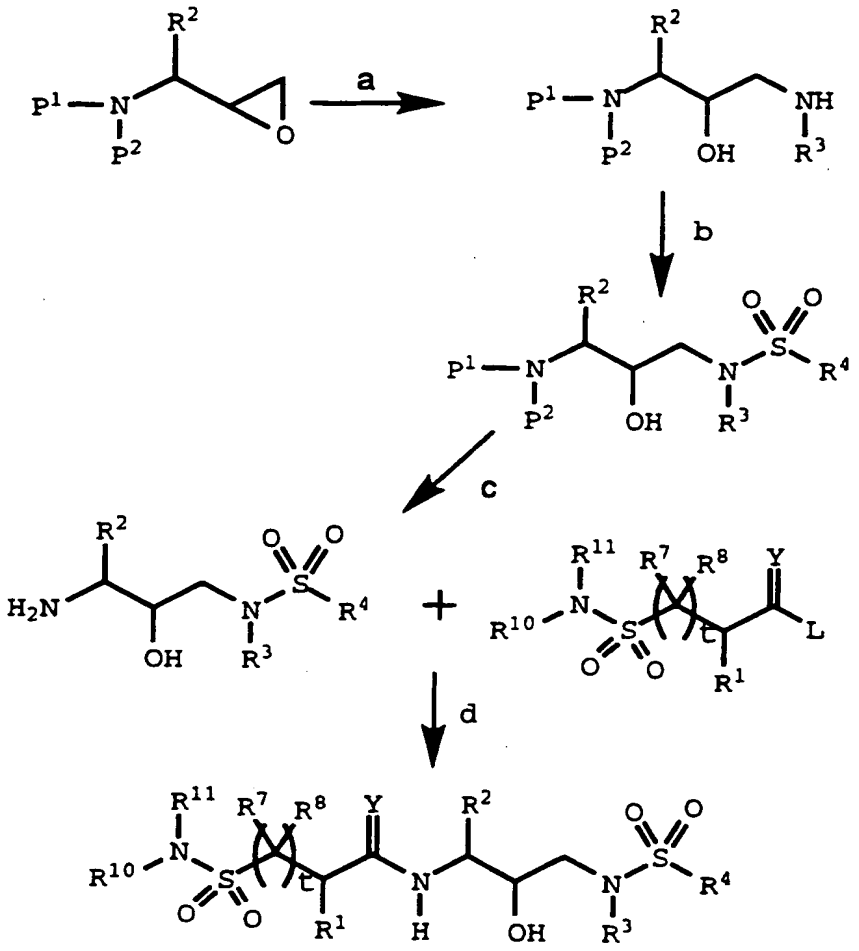
heteroaryl, heteroaralkyl, amidino, N-alkylamidino, alkoxycarbonylamino, alkylsulfonylamino and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by hydroxy, alkyl, aralkoxycarbonyl, alkanoyl, heteroaralkyl, phenyl or phenylalkyl and/or on a tertiary nitrogen atom (i.e., =N-) by oxido. "Heterocycloalkyl" means an alkyl radical as defined above in which at least one hydrogen atom is replaced by a heterocyclo radical as defined above, such as pyrrolidinylmethyl, tetrahydrothienylmethyl, pyridylmethyl and the like. The term "heteroaryl", alone or in combination, means an aromatic heterocyclo radical as defined above, which is optionally substituted as defined above with respect to the definitions of aryl and heterocyclo. Examples of such heterocyclo and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, (e.g., 2-(1-piperidinyl)pyridyl and 2-(4-benzyl piperazin-1-yl-1-pyridinyl, etc.), pyrazinyl, pyrimidinyl, furyl, tetrahydrofuryl, thienyl, tetrahydrothienyl and its sulfoxide and sulfone derivatives, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, ß-carbolinyl, 2-benzofurancarbonyl, 1-,2-,4- or 5-benzimidazolyl, methylenedioxyphen-4-yl, methylenedioxyphen-5-yl, ethylenedioxyphenyl, benzothiazolyl, benzopyranyl, benzofuryl, 2,3-dihydrobenzofuryl, benzoxazolyl, thiophenyl and the like. The term "heteroatom" means a nitrogen, oxygen or sulfur atom. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein

triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate. The term "amino acid side chain" means the side chain group, including the stereochemistry of the carbon to which it is attached, attached to the naturally occurring amino acid which distinguishes the amino acid from glycine. For example, the amino acid side chain of alanine is methyl, of histidine is imidazolylmethyl and phenylalanine is benzyl, and the attachment of such side chains to the compound of this invention retain the naturally occurring stereochemistry of the carbon to which it is attached. The following example illustrates the definition:



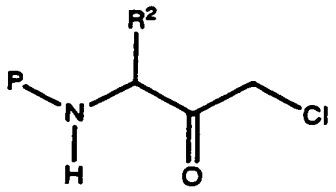
Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry of the hydroxyl group can be utilized to produce those having the (S) stereochemistry. A compound having the (R) stereochemistry of the hydroxyl group can be inverted to the (S) stereochemistry using well-known methods. For example, the hydroxy group can be converted into a leaving group such as a mesylate or tosylate and reacting the leaving group with an oxide anion such as hydroxide,

SCHEME II



a) R^3NH_2; b) R^4SO_2Cl (or anhydride) + acid scavenger; c) deprotection; and d) coupling.

An N-protected chloroketone derivative of an amino acid having the formula:



wherein P represents an amino protecting group, and R^2 is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. Alternatively, the corresponding N-protected bromoketone can also be used and is especially useful for producing some chiral alcohols. The N-protected chloroketones are commercially available, e.g., such as from Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

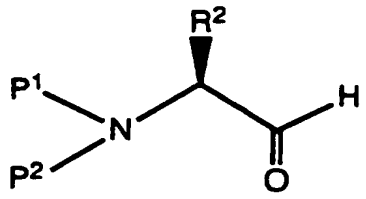
The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of the formula:

optionally substituted with halogen, alkyl of C_1-C_8, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals containing cycloalkyls of C_6-C_{10}. Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, trifluoroacetyl, tri-chloroacetyl, phthaloyl and the like.

Additionally, the P^1 and/or P^2 protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bis-disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a

then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



wherein P^1, P^2 and R^2 are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydro thiophene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, dimethylphosphoryl chloride and DMSO and isobutyl chloroformate and DMSO. The oxidation conditions reported by Reetz et al [Angew Chem., 99, p. 1186, (1987)], Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987) employed oxalyl chloride and DMSO at -78°C.

The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need

The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or sodium or potassium or calcium in ammonia. The reaction temperature may be from about -35°C to about 45°C, and preferably from abut 5°C to about 25°C. In the case of liquid amonia, the preferred temperature is about -33°C. Two additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde is accomplished by a catalytic amount of tetrapropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

Alternatively, an acid chloride derivative of a protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund Reduction).

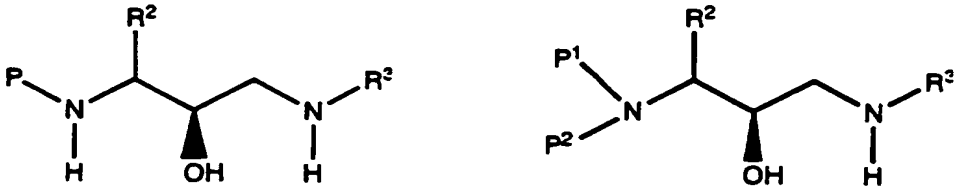
The aldehyde resulting from the Swern oxidation is then reacted with a halomethyllithium reagent, which reagent is generated <u>in situ</u> by reacting an alkyllithium or arylithium compound with a dihalomethane represented by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to -78° C and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:

conditions. The preferred pressure of the reaction is atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

Alternative methods of conversion to the epoxides of this invention include substitution of other charged methylenation precurser species followed by their treatment with base to form the analogous anion. Examples of these species include trimethylsulfoxonium tosylate or triflate, tetramethylammonium halide, methyldiphenylsulfoxonium halide wherein halide is chloride, bromide or iodide.

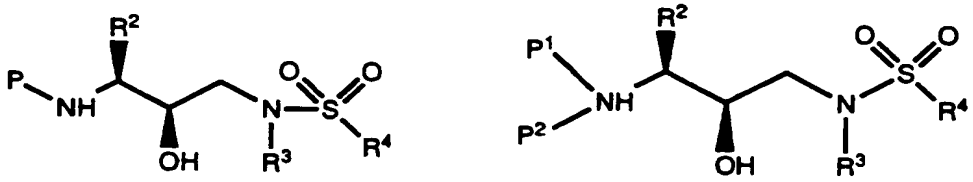
The conversion of the aldehydes of this invention into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, oxidation of the resulting protected aminosulfide alcohol with well known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, methyl tosylate, methyl mesylate, methyl triflate, ethyl bromide, isopropyl bromide, benzyl chloride or the like, in the presence of an organic or inorganic base Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, to provide a sulfonium salts that are subsequently converted into the subject epoxides with tert-amine or mineral bases.

The desired epoxides formed, using most preferred conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically and enantiomerically pure product but it is more conveniently used directly without purification to prepare retroviral protease inhibitors. The foregoing process is applicable to mixtures of optical isomers as well as



wherein P, P^1, P^2, R^2 and R^3 are as described above. Alternatively, a haloalcohol can be utilized in place of the amino epoxide.

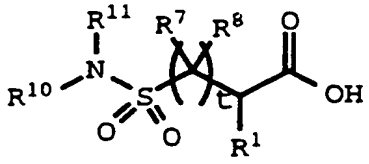
The amino alcohol defined above is then reacted in a suitable solvent with a sulfonyl chloride (R^4SO_2Cl) or sulfonyl anhydride in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran. Suitable acid scavengers include triethylamine, pyridine. Preferred sulfonyl chlorides are methanesulfonyl chloride and benzenesulfonyl chloride. The resulting sulfonamide derivative can be represented, depending on the epoxide utilized by the formulas



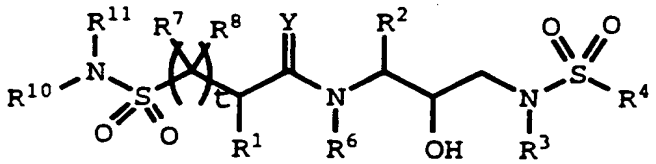
wherein P, P^1, P^2, R^2, R^3 and R^4 are as defined above. These intermediates are useful for preparing inhibitor compounds of the present invention and are also active inhibitors of retroviral proteases.

The sulfonyl halides of the formula R^4SO_2X can be prepared by the reaction of a suitable Grignard or alkyl lithium reagent with sulfuryl chloride, or sulfur dioxide followed by oxidation with a halogen, preferably chlorine. Also, thiols may be oxidized to sulfonyl chlorides using chlorine in the presence of water under carefully controlled conditions. Additionally, sulfonic

acid, thiocarboxylic acid or corresponding derivative thereof represented by the formula

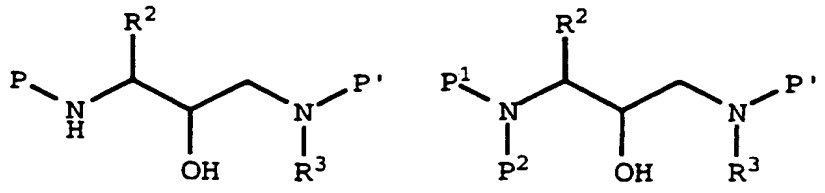


wherein t, R^1, R^7, R^8, R^{10} and R^{11} are as defined above, to produce the antiviral compounds of the present invention having the formula:



wherein t, R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^{10} and R^{11} are as defined above. Preferred protecting groups in this instance are a benzyloxycarbonyl group or a t-butoxycarbonyl group.

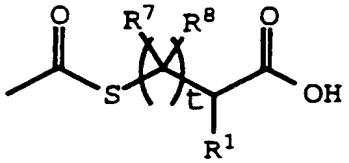
Alternatively, the coupling order may be reversed as shown in Scheme III. The protected amino alcohol from the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One skilled in the art can choose appropriate combinations of P and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formulas



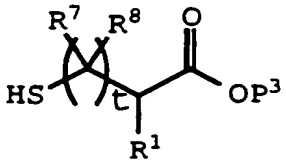
can be carried through the remainder of the synthesis to provide a compound of the formula

wherein R^1, R^7, R^8, R^{10}, R^{11} and P^3 are as defined above. This process can also be used in the asymmetric synthesis of starting materials having asymmetric centers.

The protected S-acetylthioalkylcarboxylic acids can be readily prepared using standard procedures from the corresponding substituted S-acetylthioalkylcarboxylic acids



or can be readily prepared by acetylating the corresponding substituted thiols



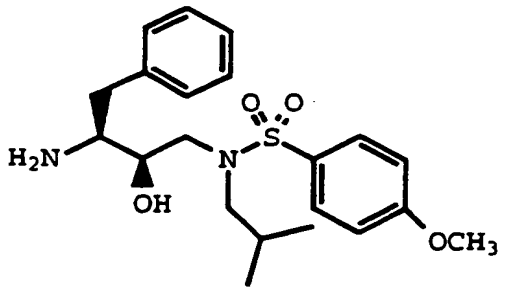
with acetic anhydride, acetyl chloride or the like using standard conditions. Such substituted thiols can be readily prepared from commercially available starting materials using standard procedures and reagents well known in the art. For example, a carbonyl can be readily converted into a thiocarbonyl which can be reduced to a thiol or reacted with a nucleophile to form a substituted thiol. Alternatively, a carboxylic acid or ester having a leaving group, such as chlorine atom, bromine atom, tosylate, mesylate and the like, can be reacted with sulfide anion, benzylthiol followed by debenzylation, thiocyanide anion followed by decyanation, and the like, to form the thiol, or with thioacetate anion to form the acetylthio derivative. In addition, Michael addition of sulfide anion on this acetate to a double bond containing carboxylic acid or protected carboxylic acid can provide the desired thioalkyl carboxylic acid. Substituted thioalkylcarboxylic acids having chiral centers can be prepared from sugars using standard synthetic methods, or

one hydrogen, can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the inhibitor compounds.

Contemplated equivalents of the general formulas set forth above for the antiviral compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all

Example 1



Preparation of 3S-amino-1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-4-phenyl-2R-butanol

Part A: N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol

To a solution of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone (75 g, 0.2 mol) in a mixture of 800 mL of methanol and 800 mL of tetrahydrofuran was added sodium borohydride (13.17 g, 0.348 mol, 1.54 equiv.) over 100 min. The solution was stirred at room temperature for 2 hours and then concentrated *in vacuo*. The residue was dissolved in 1000 mL of ethyl acetate and washed with 1N $KHSO_4$, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. The crude product was dissolved in 1000 mL of hexanes at 60°C and allowed to cool to room temperature where upon crystals formed that were isolated by filtration and washed with copious amounts of hexanes. This solid was then recrystallized from hot ethyl acetate and hexanes to provide 32.3 g 43% of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C, FAB MS: MLi^+ = 340.

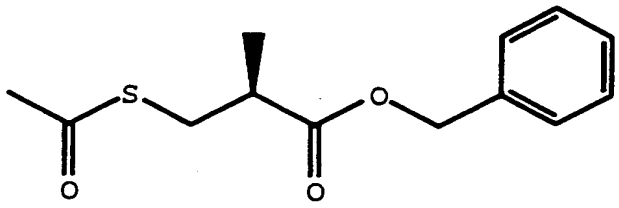
Part B: 3(S)-[N-(benzyloxycarbonyl)amino]-1,2(S)-epoxy-4-phenylbutane

A solution of potassium hydroxide (6.52 g. 0.116 mol, 1.2 equiv.) in 970 mL of absolute ethanol was treated with N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol

Part E: 3S-amino-1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-4-phenyl-2R-butanol

A solution of phenylmethyl [2(R)-hydroxy-3-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]1-S-(phenylmethyl) propyl carbamate (671.1 mg, 1.31 mmol) from Part D in 10 mL of methanol was hydrogenated over 50 mg of 10% palladium on carbon at 40 psig at room temperature for 15 hours. The catalyst was removed by filtration through diatomaceous earth and the filtrate concentrated to give a white foam, 474.5 mg, 96%, FAB MS: MH^+ = 377.

Example 2



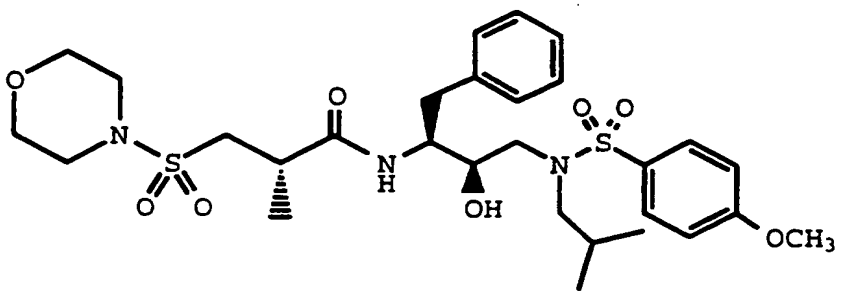
Preparation of benzyl D-(-)-S-acetyl-β-mercaptoisobutyrate

A 250 mL round bottom flask equipped with N_2 inlet, magnetic stir bar, and addition funnel was charged with 14 g D-(-)-S-acetyl-β-mercaptoisobutyric acid and 125 mL dry toluene and cooled to 0°C. To the stirring solution was added 13.6 g (1.0 eq) DBU dropwise over 20 minutes then 15.3 g (1.05 eq) benzyl bromide over about 5 minutes. The reaction was allowed to warm to room temperature overnight. The reaction was concentrated *in vacuo* and partition between ethyl acetate/saturated aqueous bicarbonate. The organic phase was washed with brine, dried, and concentrated *in vacuo* to 20.6 g (95%) benzyl D-(-)-S-acetyl-β-mercaptoisobutyrate suitable for use in the next step.

concentrated *in vacuo* and the residue was partioned between ethyl acetate/H_2O. The organic phase was washed with brine, dried and concentrated *in vacuo* to yield 10g (77%) of a white crystalline solid of benzyl 3-(1-morpholinosulfonyl)-2(R)-methylpropionate.

Part B: 3-(1-morpholinosulfonyl)-2(R)-methylpropionic acid
A 100 mL Fisher/Porter vessel was charged with 1.0 g benzyl 3-(1-morpholinosulfonyl)-2(R)-methylpropionate in 15 mL MeOH and a catalytic amount of 10% Pd-C and hydrogenated overnight at 40 psi. The next day the reaction was filtered through Celite and concentrated *in vacuo* to yield 750 mg of 3-(1-morpholinosulfonyl)-2(R)-methylpropionic acid. HRMS calcd. for $C_8H_{15}NO_5S$ calcd. 238.0748, obs 238.0760.

Example 5

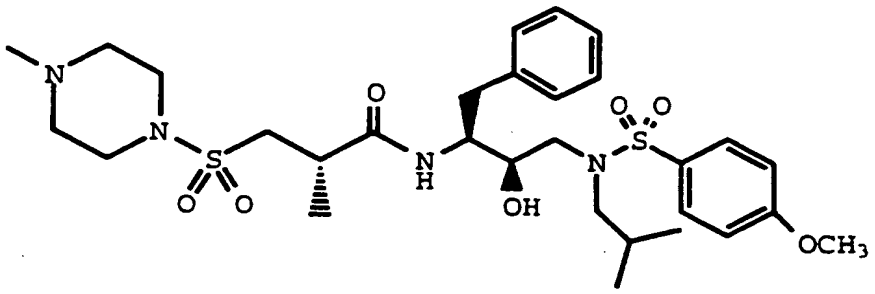


Preparation of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-(1-morpholinosulfonyl)-2(R)-methylpropionamide

A 50 mL round bottom flask equipped with magnetic stir bar was charged with 125 mg of 3-(1-morpholinosulfonyl)-2(R)-methylpropionic acid from Example 4 in 5 mL DMF. The solution was cooled to 0°C and 107 mg (1.5 eq) HOBT was added followed by 112 mg (1.1 eq) EDC. After 30 minutes, 200 mg of amine from Example 1 (0.93 eq) in 2 mL DMF was added and the reaction was stirred at room temperature overnight. The reaction was concentrated *in vacuo* and the

A 100 mL Fisher/Porter vessel was charged with benzyl 3-[(4-methylpiperizin-1-yl)sulfonyl]-2(R)-methylpropionate in 15 mL MeOH with a catalytic amount of 10% Pd-C. Hydrogenation at 50 psi for 48 hours afforded, after filtration through Celite and concentration *in vacuo* to yield 3-[(4-methylpiperizin-1-yl)sulfonyl]-2(R)-methylpropionic acid as a hygroscopic foam suitable for use without further purification.

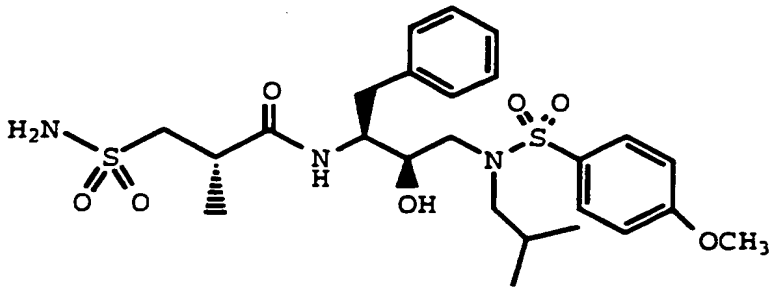
Example 7



Preparation of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[(4-methylpiperizin-1-yl)sulfonyl]-2(R)-methylpropionamide

A 100 mL round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 79 mg of 3-[(4-methylpiperizin-1-yl)sulfonyl]-2(R)-methylpropionic acid from Example 6 (1.15 eq) in 5 mL DMF. The solution was cooled to 0°C and 55 mg (1.5 eq) HOBt was added followed by 61 mg (1.15 eq) EDC. After 30 minutes a solution of 110 mg amine from Example 1 in 1 mL DMF was added and the reaction was stirred at room temperature. The reaction was poured into H_2O and the product extracted with ethyl acetate. The organic phase was washed with saturated aqeous bicarbonate, brine, dried and concentrated *in vacuo* to yield crude product. Purification by flash chromatography (CH_2Cl_2/MeOH) yielded 100 mg (57%) of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-

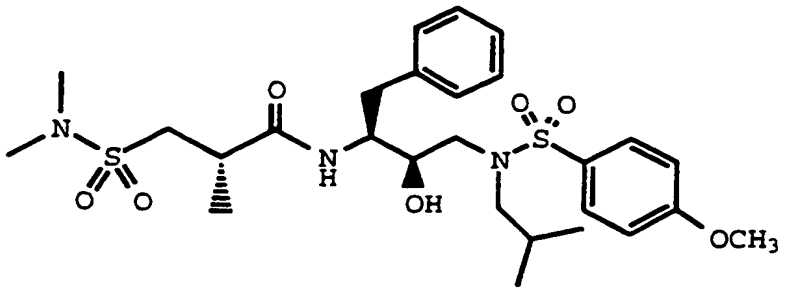
Example 9



Preparation of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-aminosulfonyl-2(R)-methylpropionamide

A 25 mL round bottom flask equipped with magnetic stir bar and N_2 inlet was charged with 70 mg of 3-aminosulfonyl-2(R)-methylpropionic acid from Example 8 in 2 mL DMF. The solution was cooled to 0°C and charged with 74 mg (1.5 eq) HOBt, and 80 mg (1.15 eq) EDC. After 15 minutes a solution of 147 mg of amine from Example 1 in 2 mL DMF was added. The reaction was stirred 20 hours at room temperature and partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phase was washed with brine, dried and concentrated *in vacuo* to yield 160 mg of crude oil. The crude material was dissolved in ethyl acetate, washed with 10% aq $KHSO_4$ and concentrated *in vacuo* to yield 80 mg crude product. Purification by flash chromatography (MeOH/ethyl acetate) on silica gel afforded 35 mg of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-aminosulfonyl-2(R)-methylpropionamide. HRMS calcd. for $C_{24}H_{36}N_3O_7S_2$; calcd. 556.2151, obs. 556.2198.

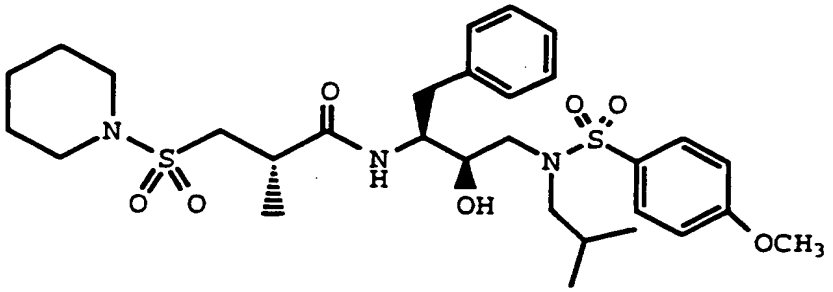
Example 11



Preparation of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[(dimethylamino)sulfonyl]-2(R)-methylpropionamide

A 50 mL round bottom flask equipped with magnetic stir bar was charged with 126 mg of 3-[(dimethylamino)sulfonyl]-2(R)-methylpropionic acid from Example 10 in 2 mL DMF. The solution was cooled to 0°C and 110 mg (1.5 eq) HOBt was added followed by 124 mg (1.15 eq) EDC. After 30 minutes, 236 mg of amine from Example 1 in 3 mL DMF was added. The reaction was stirred at room temperature overnight. The reaction was partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phase was washed with brine, dried and concentrated *in vacuo* to yield 220 mg crude product. Flash chromotography (3% MeOH/CH_2Cl_2) on silica gel gave 84 mg (25%) of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[(dimethylamino)sulfonyl]-2(R)-methylpropionamide. HPLC indicators 99.2% pure. HRMS calcd. for (M+Li) $C_{27}H_{41}N_3O_7S_2$: calcd. (M+Li) 590.2546, obs (m+Li) 590.2599.

Example 13



Preparation of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-(1-piperidinyl)sulfonyl-2(R)-methylpropionamide

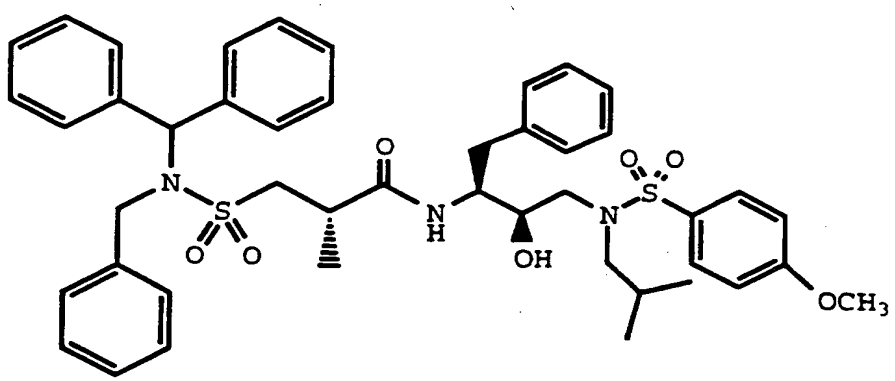
A 50 mL round bottom flask equipped with magnetic stir bar was charged with 100 mg of 3-(1-piperidinyl)sulfonyl-2(R)-methylpropionic acid in 3 mL DMF. The solution was cooled to 0°C and 75 mg (1.5 eq) HOBt added followed by 82 mg (1.15 g) EDC. After 30 minutes, 172 mg of amine from Example 1 in mL DMF was added. The reaction was stirred 20 hours at room temperature then partitioned between ethyl acetate and saturated aqueous bicarbonate. The organic phase was washed with brine, dried, and concentrated *in vacuo* to yield 180 mg of crude product. Flash chromatography yielded 60 mg of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-(1-piperidinyl)sulfonyl-2(R)-methylpropionamide. HRMS calcd. for $C_{30}H_{45}N_3O_7S_2O$: calcd. 624.2777, obs. 624.2753.

of a clear oil. Flash chromatography on silica gel (30% ethyl acetate/hexanes) afforded 730 mg of methyl 3-[N-(benzyl)-N-(diphenylmethyl)aminosulfonyl]-2(R)-methylpropionate. HRMS (M+Li): calcd. 444.1821, obs 444.1865.

Part C: 3-[N-(benzyl)-N-(diphenylmethyl)aminosulfonyl]-2(R)-methylpropionic acid

A 50 mL round bottom flask equipped with magnetic stir bar was charged with 320 mg of methyl 3-[N-(benzyl)-N-(diphenylmethyl)aminosulfonyl]-2(R)-methylpropionate and 120 mg LiOH (4 eq) in 4 mL 50% aq THF. After 5 minutes 2 mL MeOH added to get homogeneous solution, after 1 hour the reaction was partioned between ethyl acetate and 5% aq $KHSO_4$. The organic phase was washed with brine, dried, and concentrated *in vacuo* to yield 250 mg of 3-[N-(benzyl)-N-(diphenylmethyl)aminosulfonyl]-2(R)-methylpropionic acid as a clear semi-solid. HRMS (M+Li): calcd. 430.1664, obs. 430.1698.

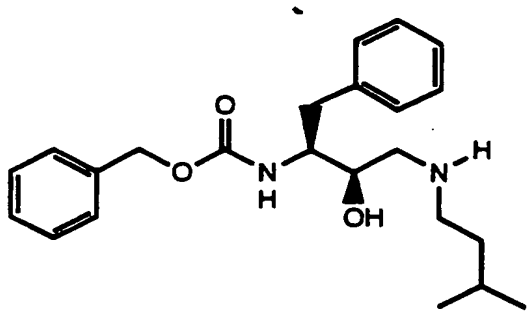
Example 15



Preparation of N1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[N-(benzyl)-N-(diphenylmethyl)aminosulfonyl]-2(R)-methylpropionamide

through Celite the residue was flash chromatographed on silica gel (100% H -> 100% EA) to afford 170 mg of N^1-[1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[N-(benzyl)aminosulfonyl]-2(R)-methylpropionamide. HRMS (M+Li): calcd. 652.2703, obs. 652.2747.

Example 17

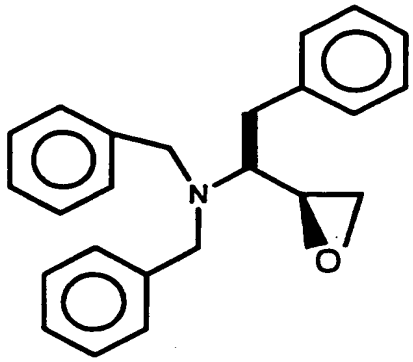


Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isoamylamine

Part A:

To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate

Example 18



Preparation of N,N-dibenzyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane

Step A:

A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) was heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) was then slowly added (addition time ~25 min). The mixture was then stirred at 97°C for 30 minutes. The solution was cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers were then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product was then used in the next step without purification.

Step B:

The crude benzylated product of the above step was dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) was then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The mixture was stirred for 20 minutes at -55°C. The reaction was quenched at -55°C by the slow addition of methanol (37 ml). The cold solution was then poured into

product was diluted with 2.0 L of tap water and stirred for 5 minutes to dissolve the inorganic by products. The product was isolated by filtration under reduced pressure and washed with water until the pH is 7. The crude product obtained was air dried overnite to give a semi-dry solid (407 g) which was recrystallized from 1.1 L of ethyl acetate/heptane (1:10 by volume). The product was isolated by filtration (at -8°C), washed with 1.6 L of cold (-10°C) ethyl acetate/heptane (1:10 by volume) and air-dried to give 339 g (88% yield) of ßS-2-[Bis(phenylmethyl)amino]benzene-propanol, mp 71.5-73.0°C. More product can be obtained from the mother liquor if necessary. The other analytical characterization was identical to compound prepared as described above.

Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) was cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) was then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture was stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time ~20 min., temp. -75°C to -68°C). The solution was stirred at -78°C for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) was then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture was stirred for 30 min. and then water (225 ml) was added. The dichloromethane layer was separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue was diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate was concentrated to give the desired aldehyde product. The

Pirkle—Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of the desired S-isomer: 8.75 min., retention time of the R-enanatiomer 10.62 min.

Step D:

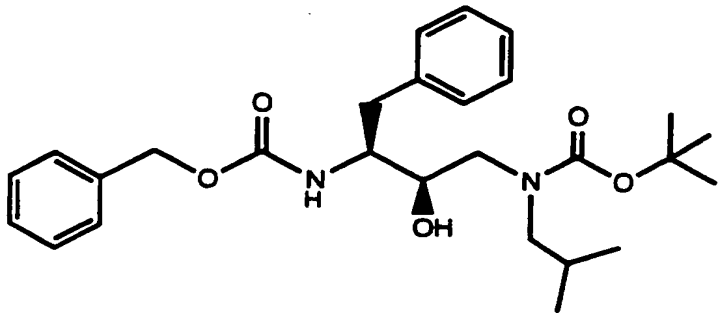
A solution of αS-[Bis(phenylmethyl)amino] benzene-propanaldehyde (191.7 g, 0.58 mol) and chloroiodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 365 mL, 0.58 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional chloroiodomethane (17 mL) was added, followed by n-butyllithium (110 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (55 mL, 0.088 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (37 mL, 0.059 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with

^{1}H NMR (300 MHz, $CDCl_3$) ∂ 2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H).HPLC on chiral stationary phase: Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of(8): 9.38 min., retention time of enanatiomer of (4): 13.75 min.

Alternatively, a solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to -78°C, under a nitrogen atmosphere. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) was added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture was stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at -75°C. The cooling bath was then removed and the solution warmed to 22°C over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer was separated. The aqueous phase was extracted with ethyl acetate (1 x 300 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step. The product could also be purified by chromatography.

layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material.

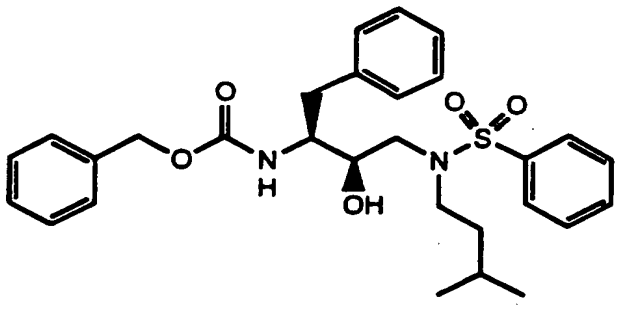
Example 19



Preparation of N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl]butane

To a solution of 7.51g (20.3 mmol) of N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)]amine in 67 mL of anhydrous tetrahydrofuran was added 2.25g (22.3 mmol) of triethylamine. After cooling to 0°C, 4.4g (20.3 mmol) of di-tert-butyldicarbonate was added and stirring continued at room temperature for 21 hours. The volatiles were removed in vacuo, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 9.6g of crude product. Chromatography on silica gel using 30% ethyl acetate/hexane afforded 8.2g of pure N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl]butane, mass spectum m/e = 477 (M+Li).

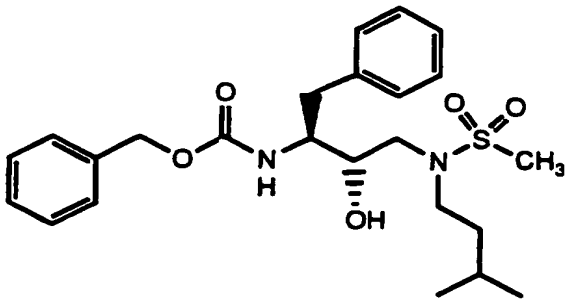
Example 21



Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

From the reaction of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8 mmol) one obtains phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-carbamate. Column chromotography on silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for $C_{29}H_{36}N_2O_5S$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37; H, 6.93; N, 5.26.

Example 23



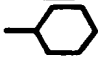
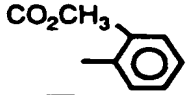
Preparation of phenylmethyl [2S-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

To a solution of N-[3(S)-benzyloxycarbonylamino-2(S)-hydroxy-4-phenylbutyl]-N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 0.55 mmol) in dichloromethane (8 mL) was added dropwise methanesulfonyl chloride (39 uL, 0.55 mmol). The reaction mixture was stirred for 16 hours at room temperature, then the dichloromethane solution was applied to a silica gel column (50 gm). The column was eluted with dichloromethane containing 2.5% methanol. The phenylmethyl [2S-hydroxy-3-[(3-methylbutyl)(methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white solid Anal. Calcd. for $C_{24}H_{34}N_2O_5S \cdot 0.2\ H_2O$: C, 61.83; H, 7.44; N, 6.01. Found: C, 61.62; H, 7.40; N, 5.99.

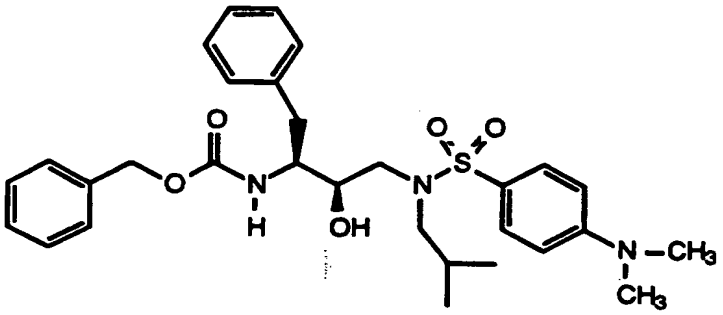
Example 24

Following the procedures of the previous Examples 1-23, the compounds set forth in Table 1A were prepared.

TABLE 1A (Cont'd)

Entry	R^3	R^4
24	-CH_2-  -F	-Ph
25	-CH_2- 	-Ph
26	-CH_2-  -OCH_3	-Ph
27	-CH_2- 	-Ph
28	-CH_2- 	-Ph
29	-$CH_2CH{=}CH_2$	-Ph
30	- 	-Ph
31		-Ph
32	-CH_2CH_2Ph	-Ph
33	-$CH_2CH_2CH_2CH_2OH$	-Ph
34	-$CH_2CH_2N(CH_3)_2$	-Ph
35	-CH_2CH_2- 	-Ph
36	-CH_3	-Ph
37	-$CH_2CH_2CH_2SCH_3$	-Ph
38	-$CH_2CH_2CH_2S(O)_2CH_3$	-Ph
39	-$CH_2CH_2CH(CH_3)_2$	- 
40	-$CH_2CH_2CH(CH_3)_2$	-$CH_2CH_2CH_3$
41	-$CH_2CH_2CH(CH_3)_2$	-CH_3
42	-$CH_2CH_2CH(CH_3)_2$	-  -F
43	-$CH_2CH_2CH(CH_3)_2$	-  -CH_3
44	-$CH_2CH_2CH(CH_3)_2$	
45	-$CH_2CH(CH_3)_2$	-  -NO_2
46	-$CH_2CH(CH_3)_2$	-  -NHAc
47	-$CH_2CH(CH_3)_2$	-  -CH_3

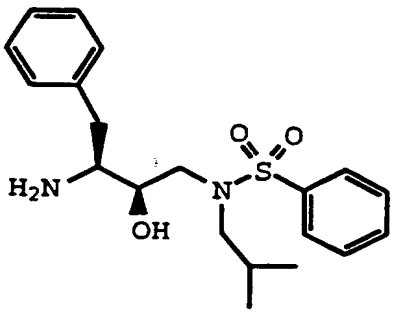
Example 25



Preparation of Carbamic acid, [2R-hydroxy-3-[[(4-dimethylaminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester

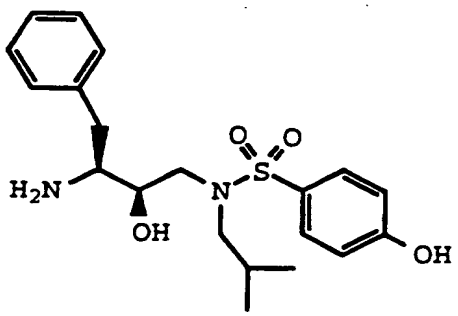
To a solution of 100mg (0.19 mmol) of carbamic acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, phenylmethyl ester in 1 mL of pyridine was added 53 µL of triethylamine and 120 µL (p.95 mmol) of 40% aqueous dimethylamine. After heating for 24 hours at 100°C, the solution was cooled, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated. The resulting solid was recrystallized from ethyl acetate/hexane to afford 10 mg of the desired product; mass spectrum m/e = 540 (M+H).

Example 26



solution concentrated to afford 352 mg of [2R-hydroxy-3-[(phenylsulfonyl])2-methylpropyl)amino]-1S-(phenylmethyl) propylamine, mass spectrum m/e = 377 (M+H), which was used directly in the next step without purification.

Example 27



Preparation of 1-amino-2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propane

Part A:

A solution of 0.98 g (1.85 mmol) of carbamic acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-phenylmethyl ester in 3.8 mL of anhydrous DMF was added to 22mg (7.4 mmol) of 80% sodium hydride in 2 mL of DMF. To this mixture was added 0.40g (3.7 mmol) of benzyl alcohol. After 2 hours, the solution was cooled to O C, water added, and then ethyl acetate. The organic layer was washed with 5% cirtic acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to afford 0.90g of crude material. This was chromatographed on basic alumina using 3% methanol/methylene chloride to afford 0.70g of 2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl] amino-1S-(phenylmethyl)propylamine, cyclic carbamate; mass spectrum m/e=509(M+H).

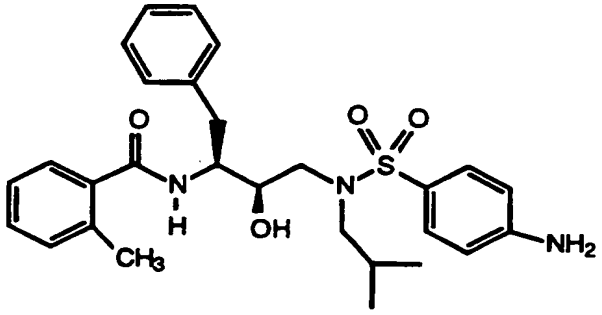
Part A: Preparation of Carbamic acid, 2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 4.0 g (10.8 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 50mL of anhydrous methylene chloride, was added 4.5mL (3.27g, 32.4 mmol) of triethylamine. The solution was cooled to 0°C and 2.63g (11.9 mmol) of 4-nitrobenzene sulfonyl chloride was added, stirred for 30 minutes at 0°C, then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 5.9 g of crude material. This was recrystallized from ethyl acetate/hexane to afford 4.7 g of pure carbamic acid, [2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester, m/e=556(M+H).

Part B: Preparation of 2R-hydroxy-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl) propylamine

A solution of 3.0g (5.4 mmol) of carbamic acid, 2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 20 mL of ethyl acetate was hydrogenated over 1.5 g of 10% palladium-on-carbon catalyst under 35 psig of hydrogen for 3.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 2.05 g of the desired 2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl) amino]-1S-(phenylmethyl)propylamine, m/e=392(M+H).

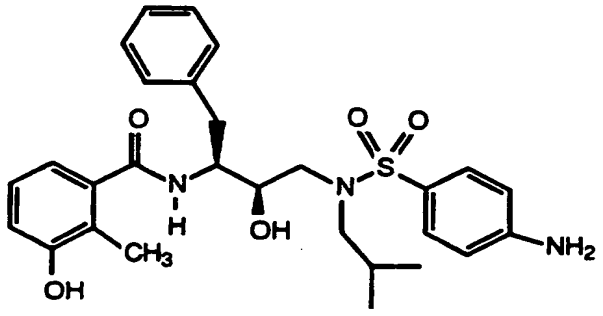
Example 30



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl

To a solution of 391 mg (1 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine in 3 mL of anhydrous methylene chloride, was added 0.42 mL (3 mmol) of triethylamine, then at room temperature, 0.12 mL (0.9 mmol) of ortho-toluoyl chloride was added. After 15 hours at room temp ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 420 mg of crude material. This was chromatographed on 40 g of silica gel using 50% ethyl acetate/hexane to afford 368 mg of pure benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl, m/e=516(M+Li).

Example 31

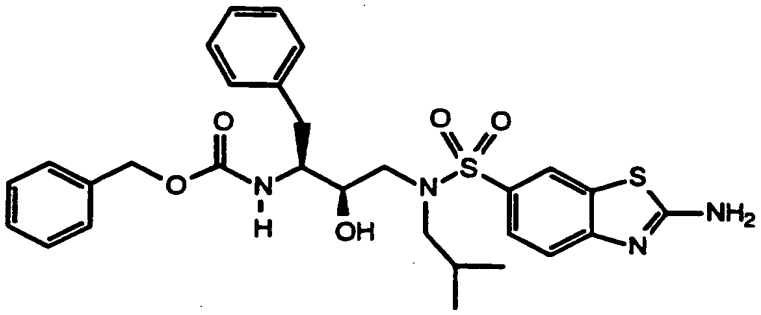


methanol/methylene chloride afforded 0.39 grams (36%) of a yellow solid.

Part B: Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl

To a solution of 175 mg (1.15 mmol) of 3-hydroxy-2-methylbenzoic acid and 203 mg (1.5 mmol) of N-hydroxybenzotriazole in 6 mL of anhydrous N,N-dimethylformamide at 0°C, was added 220 mg (1.15 mmol) of EDC. After 20 minutes of activation at 0°C and 1 hour at room temperature, 392 mg (1.0 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-aminophenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 15 hours at room temperature, ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 590 mg of crude material. This was chromatographed on silica gel using 50-80% ethyl acetate/methylene chloride as eluent to afford 255 mg of pure benzamide, N-[2R-hydroxy-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl, m/e = 526(M+H).

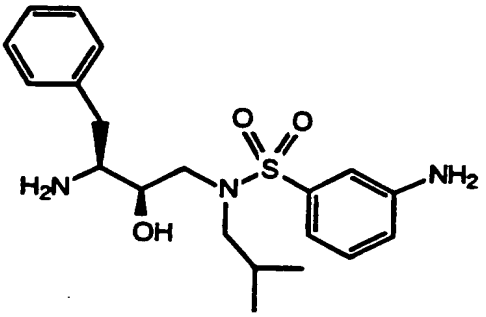
Example 32



Preparation of Carbamic acid, 2R-hydroxy-3-[[(2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

purified by chromatography (hexane:ethyl acetate 5:3) to afford 0.130 g (53%) of the desired product as a solid.

Example 34



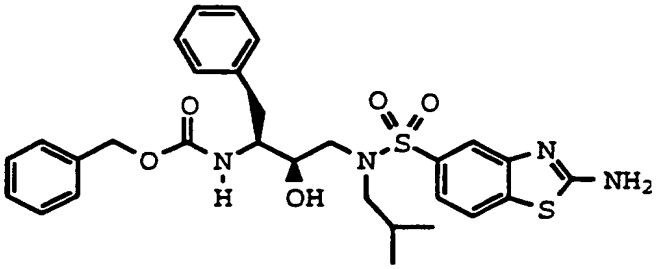
Preparation of 2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

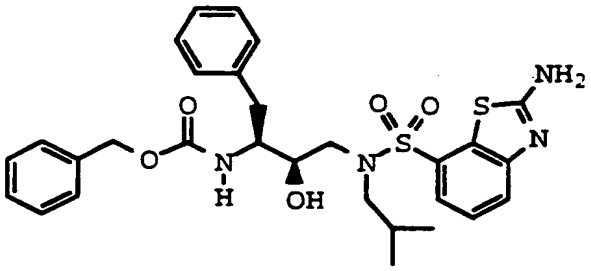
To a solution of 1.1 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 15mL of anhydrous methylene chloride, was added 1.3mL (0.94g, 9.3 mmol) of triethylamine. The solution was cooled to 0°C and 0.67 g (3.0 mmol) of 3-nitrobenzene sulfonyl chloride was added, stirred for 30 minutes at 0°C, then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.74 g of crude material. This was recrystallized from ethyl acetate/hexane to afford 1.40 g of pure carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester, m/e=562(M+Li).

citric acid, saturated sodium bicarbonate, brine, dried, filtered and concentrated to afford 330 mg of crude material. This was chromatographed on silica gel using 30-70% ethyl acetate/methylene chloride as eluent to afford 230 mg of pure benzamide, N-[2R-hydroxy-3-[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-3-hydroxy-2-methyl.

Example 36



and



Preparation of Carbamic acid, 2R-hydroxy-3-[[(2-amino benzothiazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester; and Carbamic acid, 2R-hydroxy-3-[[(2-aminobenzothiazol-7-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

The 2R-hydroxy-3-[(3-aminophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid phenylmethyl ester 0.36 g (0.685 mmol) was added to a well mixed powder of anhydrous copper sulfate (1.44 g) and potassium thiocyanate (1.80 g) followed by dry methanol (10 mL) and

recrystallized from ethyl acetate to afford 2.45 g of 5-(2,3-dihydrobenzofuranyl)sulfonyl chloride.

Part B: Preparation of Carbamic acid, 2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 1.11 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 20mL of anhydrous methylene chloride, was added 1.3mL (0.94 g, 9.3 mmol) of triethylamine. The solution was cooled to 0°C and 0.66 g of 5-(2,3-dihydrobenzofuranyl) sulfonyl chloride was added, stirred for 15 minutes at 0°C, then for 2 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.62 g of crude material. This was recrystallized from diethyl ether to afford 1.17 g of pure carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester.

Part C: Preparation of [2R-hydroxy-3-[[(2,3-dihydro benzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

A solution of 2.86 g of carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 30 mL of tetrahydrofuran was hydrogenated 0.99g of 10% palladium-on-carbon under 50 psig of hydrogen for 16 hours. The catalyst was removed by filtration and the filtrate concentrated to afford 1.99 g of the desired [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

period. The temperature was then raised to 75°C and held for 22 hours (NMR indicated that the reaction was done after 9 hours.) The reaction was cooled to 26° and oxalyl chloride (2290g, 18.1 moles) was added at a rate so as to maintain the temperature below 40°C (1.5 hours). The mixture was heated to 67°C for 5 hours followed by cooling to 16°C with an ice bath. The reaction was quenched with water (5 l) at a rate which kept the temperature below 20°C. After the addition of water was complete, the mixture was stirred for 10 minutes. The layers were separated and the organic layer was washed again twice with water (5l). The organic layer was dried with magnesium sulfate (500g) and filtered to remove the drying agent. The solvent was removed under vacuum at 50°C. The resulting warm liquid was allowed to cool at which time a solid began to form. After one hour, the solid was washed with hexane (400 mL), filtered and dried to provide the desired sulfonyl chloride (2823g). The hexane wash was concentrated and the resulting solid washed with 400 mL hexane to provide additional sulfonyl chloride (464g). The total yield was 3287g (95.5% based upon 1,3-benzodioxole).

Method 3:

1,4-benzodioxan-6-sulfonyl chloride was prepared according to the procedure disclosed in EP 583960, incorporated herein by reference.

Part B: Preparation of Carbamic acid, 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To a solution of 3.19 g(8.6 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 40mL of anhydrous methylene chloride, was added 0.87g of triethylamine. The solution was cooled to 0°C and 1.90g of (1,3-benzodioxol-5-yl)sulfonyl chloride was added,

reflux for 2 hr. About 200 mL of water was distilled off and concentration of the reaction mixture afforded a solid. The solid was filtered and was washed with cold water and air dried to afford 67.5 g (59%) of the desired product as a white powder.

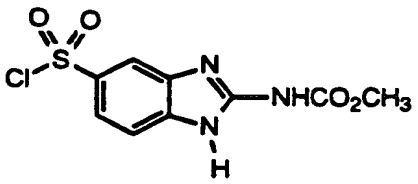
Part B: Preparation of 2-Amino-6-sulfonamidobenzothiazole

Bromine (43.20 g, 0.27 mol) in chloroform (200 mL) was added over 1 hr. to a suspension of N-(4-sulfonamidophenyl)-thiourea (27.72, 0.120 mol) in chloroform (800 mL). After the addition, the reaction mixture was heated at reflux for 4.5 hr. The chloroform was removed in vacuo and the residue was repeatedly distilled with additional amounts of chloroform. The solid obtained was treated with water (600 mL) followed by ammonium hydroxide (to make it basic), then was heated at reflux for 1 hr. The cooled reaction mixture was filtered, washed with water and air dried to afford 22.0 g (80%) of the desired product as a white powder.

Part C: Preparation of Benzothiazole-6-sulfonic acid

A suspension of 2-amino-6-sulfonamido-benzothiazole (10.0 g, 43.67 mmol) in dioxane (300 mL) was heated at reflux. Isoamylnitrite (24 mL) was added in two portions to the reaction mixture. Vigorous evolution of gas was observed (the reaction was conducted behind a shield as a precaution) and after 2 hr., a red precipitate was deposited in the reaction vessel. The reaction mixture was filtered hot, and the solid was washed with dioxane and was dried. The solid was recrystallized from methanol-water. A small amount of a precipitate was formed after 2 days. The precipitate was filtered off and the mother liquor was concentrated in vacuo to afford a pale red-orange solid (8.0 g, 85%) of pure product.

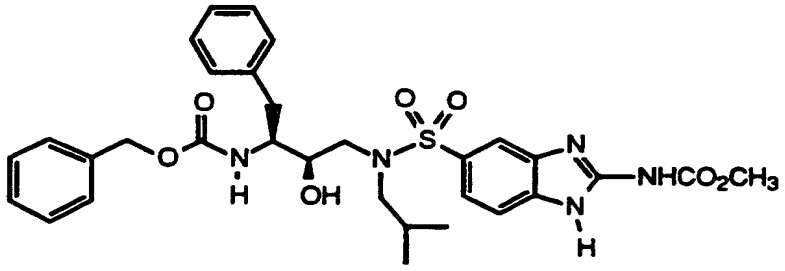
Example 41



Preparation of 5-Chlorosulfonyl-2-carbomethoxyamino-benzimidazole

A solution of 2-carbomethoxyamino-benzimidazole (5.0g, 0.026 mole) in chlorosulfonic acid (35.00 mL) was stirred at 0°C for 30 min. and at room temperature for 3 hr. The resulting dark colored reaction mixture was carefully poured into an ice-water mixture (200 mL) and stirred at room temperature for 30 min. The resulting precipitate was filtered and washed throughly with cold water (500 ml). The solid was dried overnight under high vacuum in a desiccator over NaOH pallets to yield the desired compound (5.9 g. 78%) as a grey powder. ^{1}H NMR (DMSO-*d*6) 3.89 (s, 3H), 7.55 (d, 1H, J = 8.4 Hz.) 7.65 (d, 1H, J = 8.4Hz), 7.88 (s, 1H).

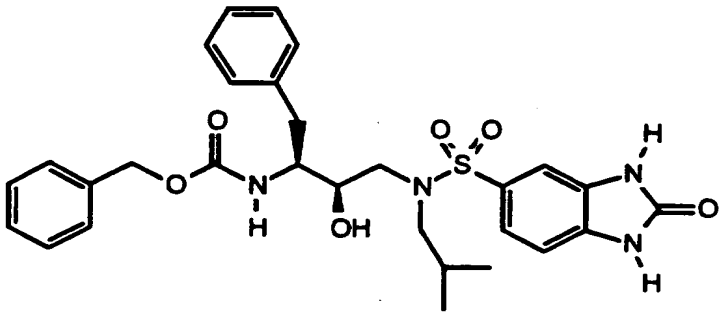
Example 42



Preparation of Carbamic acid, 2R-hydroxy-3-[[(2-carbomethoxyamino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

gummy paste formed at the bottom of the flask during the heating period. The reaction mixture was cooled to room temperature, and thionyl chloride (10.65 g, 89.5 mmoles) was added dropwise. The reaction mixture was slowly heated to 85°C and maintained at 85°C for 5 hours. As a result, the gummy paste slowly turned into a fine powder. The heterogeneous reaction mixture was then cooled to room temperature and diluted with 200 mL of dichloromethane. Water (100 mL) was added to the organic solution and a solid formed in the aqueous layer which was collected by filtration and washed with excess water and acetonitrile to give 3.9 g of a solid. The solid contained both the desired sulfonyl chloride product along with some of the corresponding sulfonic acid. The crude material was used without further purification.

Example 44



Preparation of Carbamic acid, 2R-hydroxy-3-[[(benzimidazolon-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

To N-[3S-benzyloxycarbonylamino-2R-hydroxy-4-phenylbutyl]-N-isobutylamine (1 g, 2.7 mmoles) was dissolved in 10 mL dichloromethane and then cooled to 5°C. Triethylamine (1.04 g, 10.8 mmoles) was added to the mixture. Crude 5-chlorosulfonyl-benzimidazolone (0.6 g, 2.7 mmoles) from Example 43 was added as a solid in portions to the cooled mixture. The resulting

(1.0 eq.) 4-benzylpiperazine and 1.26 mL NEt_3. The reaction was stirred for 1 hour then concentrated in vacuo and partitioned between ethyl acetate and saturated sodium bicarbonate. The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield 3.4 g crude product. Flash chromatography (80:20 ethyl acetate/hexane) yielded 3.0 g pure product.

Part B: Preparation of benzyl 3-(4-benzylpiperizin-1-yl sulfonyl)-2(R)-methylpropionic acid

A 100 mL round bottom flask equipped with magnetic stirring bar and N_2 inlet was charged with 3.0 g benzyl 3-(4-benzylpiperizin-1-ylsulfonyl)-2(R)-methylpropionate, 1.2 g LiOH (4 eq.) in 20 mL 50% aqueous methanol. After 2 hours HPLC analysis showed no starting material. The reaction was concentrated to half volume and partitioned between Et_2O and H_2O. The aqueous layer was acidified to pH 5 and extracted with 2 x 75 mL ethyl acetate. The combined organics were dried, and concentrated in vacuo to yield 550 mg (25%) white solid.

Part C: Preparation of N^1-[1-[N-(2-methylpropyl)-N-(3,4-methylenedioxyphenylsulfonyl)amino]-2(R)-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[(4-benzylpiperizin-1-yl)sulfonyl]-2(R)-methylproprionamide-HCl

A 100 mL round bottom flask equipped with magnetic stirring bar and N_2 inlet was charged with 375 mg (1.15 eq.) 3-(4-benzylpiperizin-1-ylsulfonyl)-2(R)-methylpropionic acid in 3 mL DMF. The solution was cooled to 0°C and charged with 200 mg (1.5 eq.) of HoBt followed by 220 mg (1.15 eq.) EDC. After 20 minutes at 0°C a solution of 512 mg 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine in 5 mL DMF was added and the

and stirred at this temperature for 1.5 h. The warm solution was concentrated under reduced pressure at 65°C, The brown oil resdiue was transferred to a 3-L flask and dried in vacuo (0.8 mm Hg) for 16 h to give 450 g of 3S-[N,N-bis(phenylmethyl)amino-4-phenylbutan-2R-ol as a crude oil. The product was used directly in the next step without purification. An analytical sample of the desired major diastereomeric product was obtained by purifying a small sample of crude product by silica gel chromatography (40% ethyl acetate/hexane). Tlc analysis: silica gel, 40% ethyl acetate/hexane; Rf = 0.28; HPLC analysis: ultrasphere ODS column, 25% triethylamino-/phosphate buffer pH 3-acetonitrile, flow rate 1 mL/min, UV detector; retention time 7.49 min.; HRMS calcd for $C_{28}H_{27}N_2O$ (M + 1) 417.616, found 417.2887.

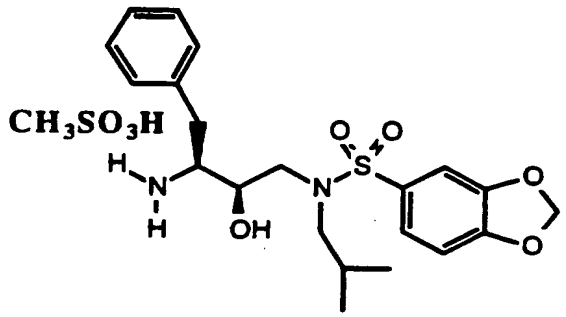
An analytical sample of the minor diastereomeric product, 3S-[N,N-bis(phenylmethyl)amino]1-(2-methylpropyl)amino-4-phenylbutan-2S-ol was also obtained by purifying a small sample of crude product by silica gel chromatography (40% ethyl acetate/hexane).

Part B: Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine•oxalic acid salt

Oxalic acid dihydrate (119g, 0.94 mole) was added to a 5000 mL round bottom flask fitted with a mechanical stirrer and a dropping funnel. Methanol (1000 ml) was added and the mixture stirred until dissolution was complete. A solution of crude 3(S)-[N,N-bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutano-2(R)-ol in ethyl acetate (1800 ml, 0.212g amino alcohol isomers/mL , 0.9428 moles) was added over a twenty minute period. The mixture was stirred for 18 hours and the solid product was isolated by centrifugation in six portions at 400G. Each portion was

mL), the solvent in the filtrate was removed under reduced pressure yielding the desired sulfonamide as an viscous yellow foamy oil (440.2g 105% yield). HPLC/MS (electrospray) (m/z 601 [M+H]+).

Example 48



Preparation of 1-[N-[(1,3-benzodioxol-5-yl)sulfonyl]-N-(2-methylpropyl)amino]-3(S)-amino-4-phenyl-2(R)-butanol•methanesulfonic acid salt

Crude 1-[N-[(1,3-benzodioxol-5-yl)sulfonyl]-N-(2-methylpropyl)amino]-3(S)-[bis(phenylmethyl)amino]-4-phenyl-2(R)-butanol (6.2g, 0.010 moles) was dissolved in methanol (40 mL). Methanesulfonic acid (0.969g, 0.010 moles) and water (5 mL) were then added to the solution. The mixture was placed in a 500 mL Parr hydrogenation bottle containing 20% $Pd(OH)_2$ on carbon (255 mg, 50% water content). The bottle was placed in the hydrogenator and purged 5 times with nitrogen and 5 times with hydrogen. The reaction was allowed to proceed at 35°C with 63 PSI hydrogen pressure for 18 hours. Additional catalyst (125 mg) was added and, after purging, the hydrogenation continued for and additional 20 hours. The mixture was filtered through celite which was washed with methanol (2 X 10 mL). Approximately one third of the methanol was removed under reduced pressure. The remaining methanol was removed by aziotropic distillation with toluene at 80 torr. Toluene was added in 15, 10, 10 and 10 mL portions. The product crystallized from the

ethyl acetate/hexane) yielded 7.2 g (90%) product as a clear oil.

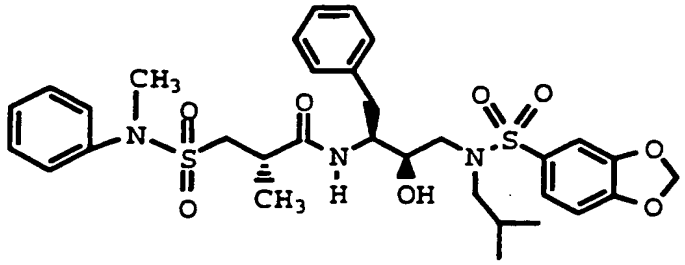
Part B: Preparation of 3-(4-tert-butoxycarbonyl piperizin-1-ylsulfonyl)-2(R)-methylpropionic acid

A 300 mL Fisher Porter vessel equipped with magnetic stirring bar was charged with 7.2 g benzyl 3-(4-tert-butoxycarbonylpiperizin-1-ylsulfonyl)-2(R)-methylpropionate, 600 mg 10% Pd-C, and 100 mL MeOH. The reaction vessel was charged with 50 psi H_2 and stirred for 2 hours at room temperature. The reaction mixture was filtered thru Celite and concentrated in vacuo to yield 5.25 g (93%) white solid. The free acid was used without further purification.

Part C: Preparation of N^1-[1-[N-(2-methylpropyl)-N-(3,4-methylenedioxyphenylsulfonyl)amino]-2(R)-hydroxy-2(S)-(phenylmethyl)prop-3-yl]-3-[4-tert-butoxycarbonylpiperizin-1-yl)sulfonyl]-2(R)-methyl proprionamide

A 250 mL round bottom flask equipped with magnetic stirring bar and N_2 inlet was charged with 4.9 g (1.0 eq.) 3-(4-tert-butoxycarbonylpiperizin-1-ylsulfonyl)-2(R)-methylpropionic acid in 100 mL DMF. The solution was cooled to 0°C and charged with 2.4 g (1.2 eq.) of HoBt followed by 2.8 g (1.0 eq.) EDC. After 20 minutes at 0°C a solution of 6.9 g (1.1 eq.) 2R-hydroxy-3-[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine in 50 mL DMF was added and the reaction was stirred at room temperature for 20 hrs. The reaction was concentrated in vacuo and partitioned between ethyl acetate and aqueous saturated bicarbonate. The combined organics were washed with 5 % aqueous citric acid, brine, dried over Na_2SO_4 and concentrated to 12.8 g crude product. Flash Chromatography

Example 50



Preparation of N-[2R-hydroxy-3-[N^1-(2-methylpropyl)-N^1-[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(N^2-methyl-N^2-phenylamino)sulfonyl]propanamide.

Part A: Preparation of Benzyl 3-(S-acetyl)-2S-methylpropionate

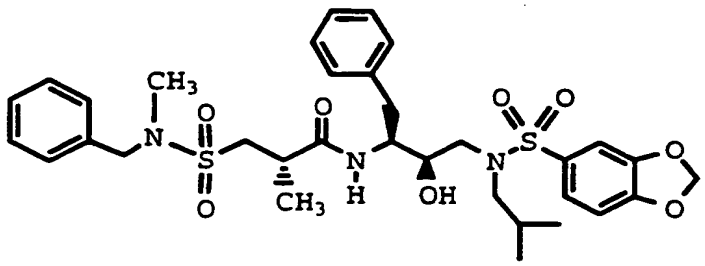
Benzyl bromide (16.5 g, 96.5 mmol) was added to a solution of 3-(S-acetyl)-2S-methylpropionic acid (13.6 g, 100 mmol) and DBU (15.2 g, 100 mmol) in toluene (200 mL). The reaction mixture was stirred at room temperature for 18 hours, diluted with toluene (200 mL), washed sequentially with 1N HCl (200 mL), sodium bicarbonate (200 mL) and brine (200 mL), dried, filtered and concentrated to afford 21 g of benzyl 3-(S-acetyl)-2S-methylpropionate.

Part B: Preparation of Benzyl 3-(chlorosulfonyl)-2S-methylpropionate

Chlorine gas was bubbled into a cold (ice-water) solution of benzyl 3-(S-acetyl)-2S-methylpropionate (10.0 g) in ethanol-chloroform (10:90, 100 mL) until a deep yellow color persisted. The reaction mixture was stirred for 30 minutes, then warmed to room temperature, concentrated and dried *in vacuo* to afford 10 g (90%) of benzyl 3-(chlorosulfonyl)-2S-methylpropionate as a colorless oil.

for 18 hours. The reaction mixture was concentrated. The resulting residue was dissolved in dichloromethane (200 mL), washed with citric acid (1N, 100 mL), sodium bicarbonate (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The residue obtained was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane (3:1) to afford 0.90 g (50%) of pure N-[2R-hydroxy-3-[N^1-(2-methylpropyl)-N^1-[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(N^2-methyl-N^2-phenylamino)sulfonyl]propanamide; FAB-MS for $C_{32}H_{41}N_3O_8S_2$: found: *m/z* = 659.

Example 51



Preparation of N-[2R-hydroxy-3-[N^1-(2-methylpropyl)-N^1-[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(N^2-methyl-N^2-benzylamino)sulfonyl]propanamide.

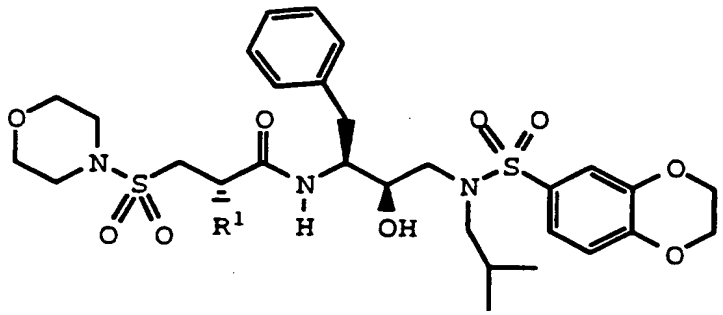
Part A: Preparation of Benzyl 3-[(N-Methyl-N-benzylamino)sulfonyl]-2S-methylpropionate

Triethylamine (1.7 mL) was added to a cooled (ice-water) solution of N-methyl-benzylamine (1.45 g, 11.98 mmol) and benzyl 3-(chlorosulfonyl)-2S-methyl-propionate (3.0 g, 10.85 mmol) in dichloromethane (30 mL). The reaction mixture was stirred for 18 hours, diluted with dichloromethane (100 mL), washed with HCl (1N, 100 mL), sodium bicarbonate (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated to

Example 52

Following the procedures of the previous Examples, the compounds set forth in Tables 2-15 can be prepared.

TABLE 2



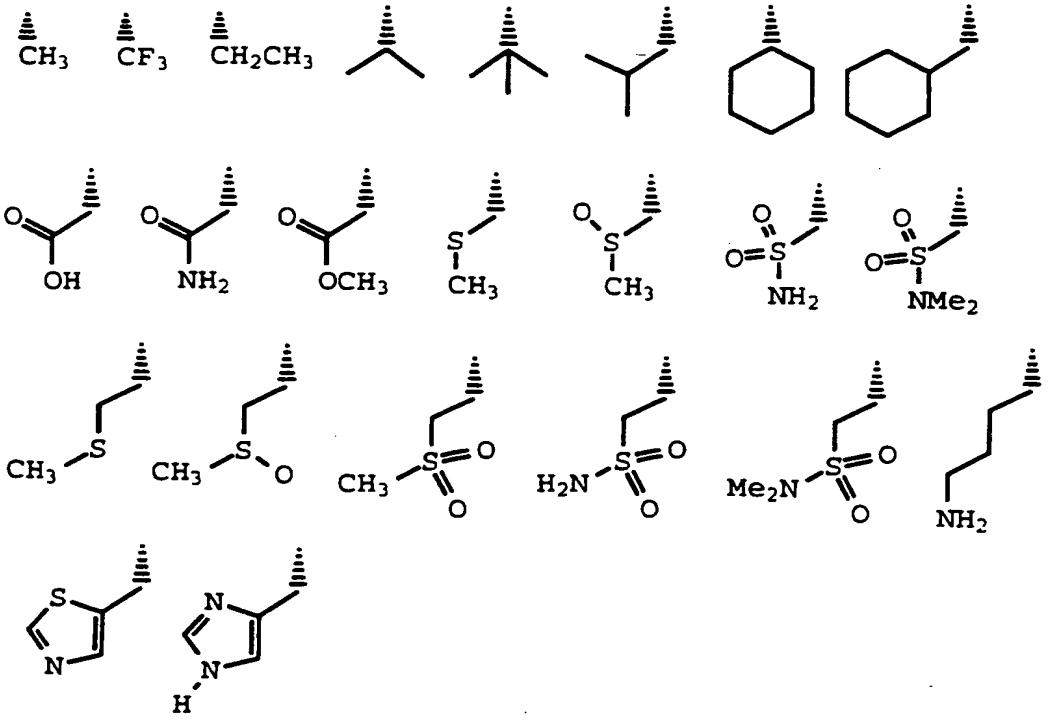
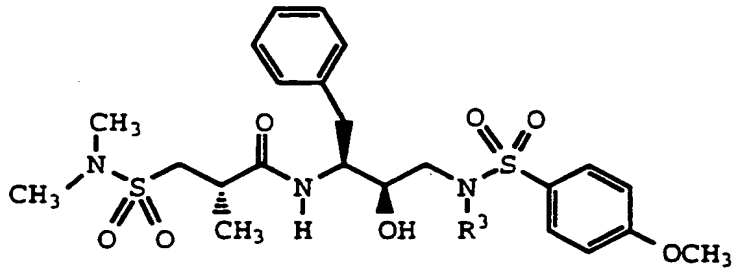
R^1


TABLE 4



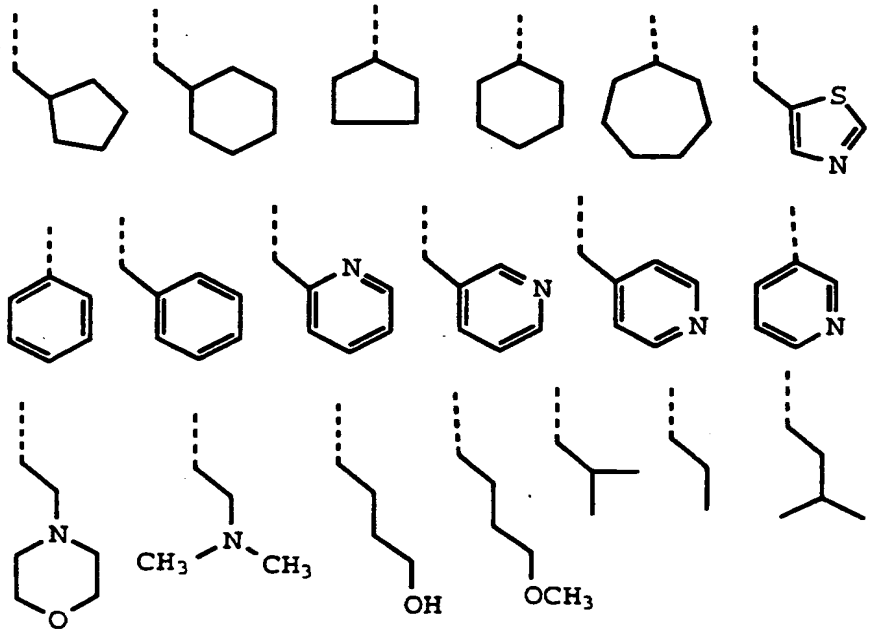
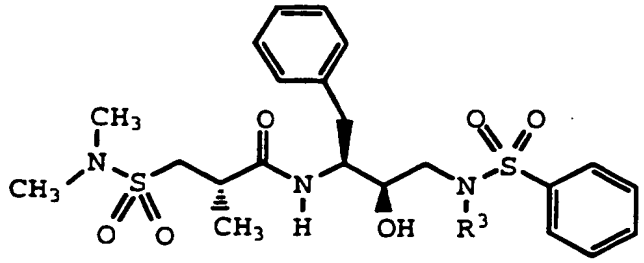
R^3


TABLE 6A



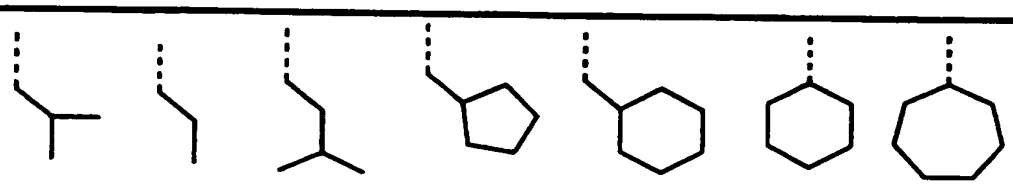
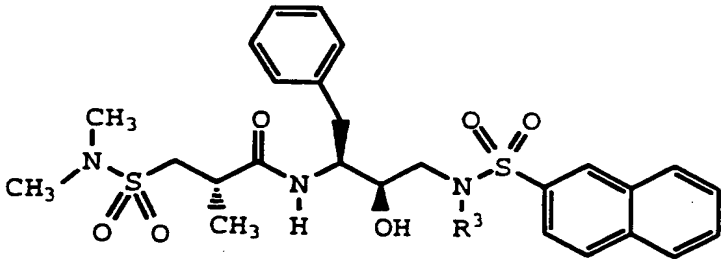
R^3


TABLE 6B



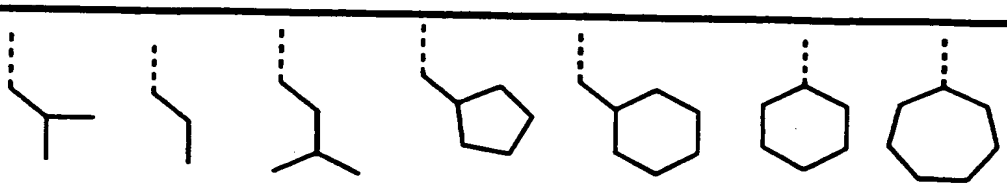
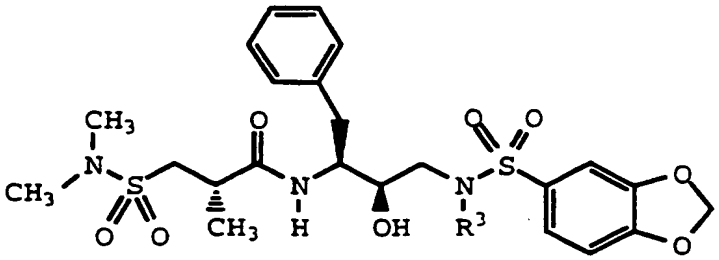
R^3


TABLE 6E



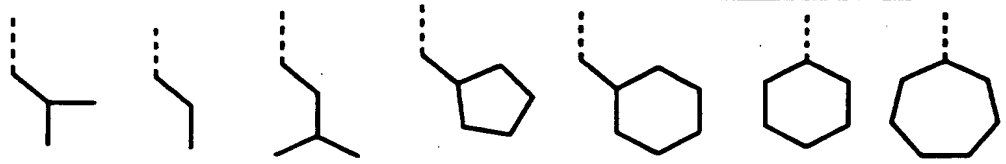
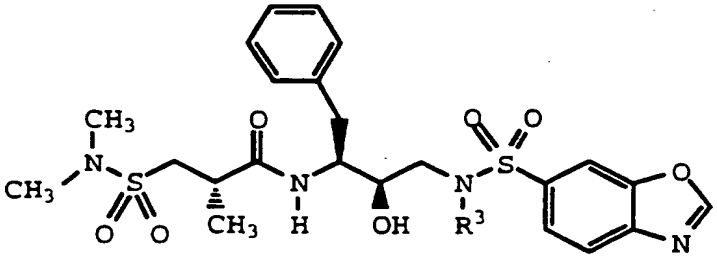
R^3


TABLE 6F



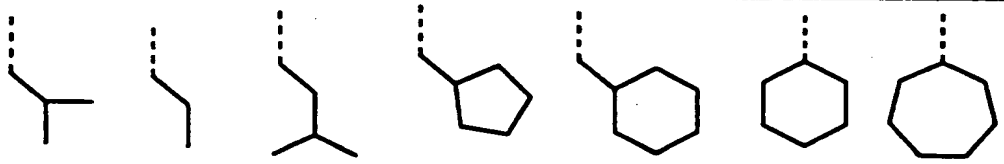
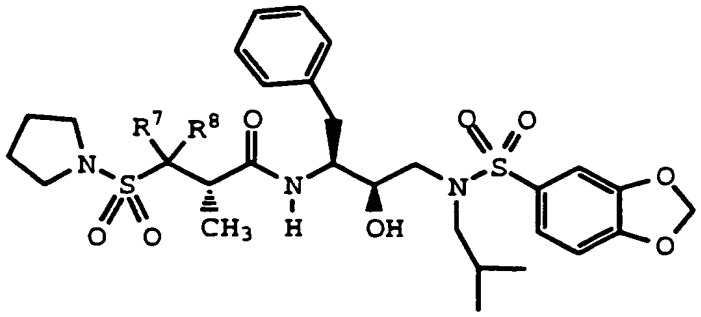
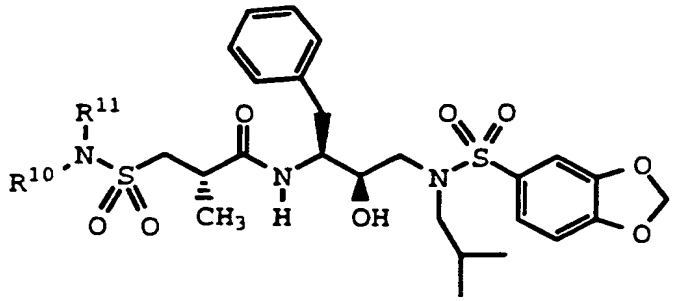
R^3


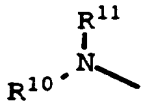
TABLE 7



R^7	R^8
H	H
CH_3	H
CH_3	H
CH_3	CH_3
phenyl	H
benzyl	H
$-C(O)NH_2$	H
$-C(NH)NH_2$	H
$-CO_2H$	H
$-CO_2CH_3$	H

TABLE 9





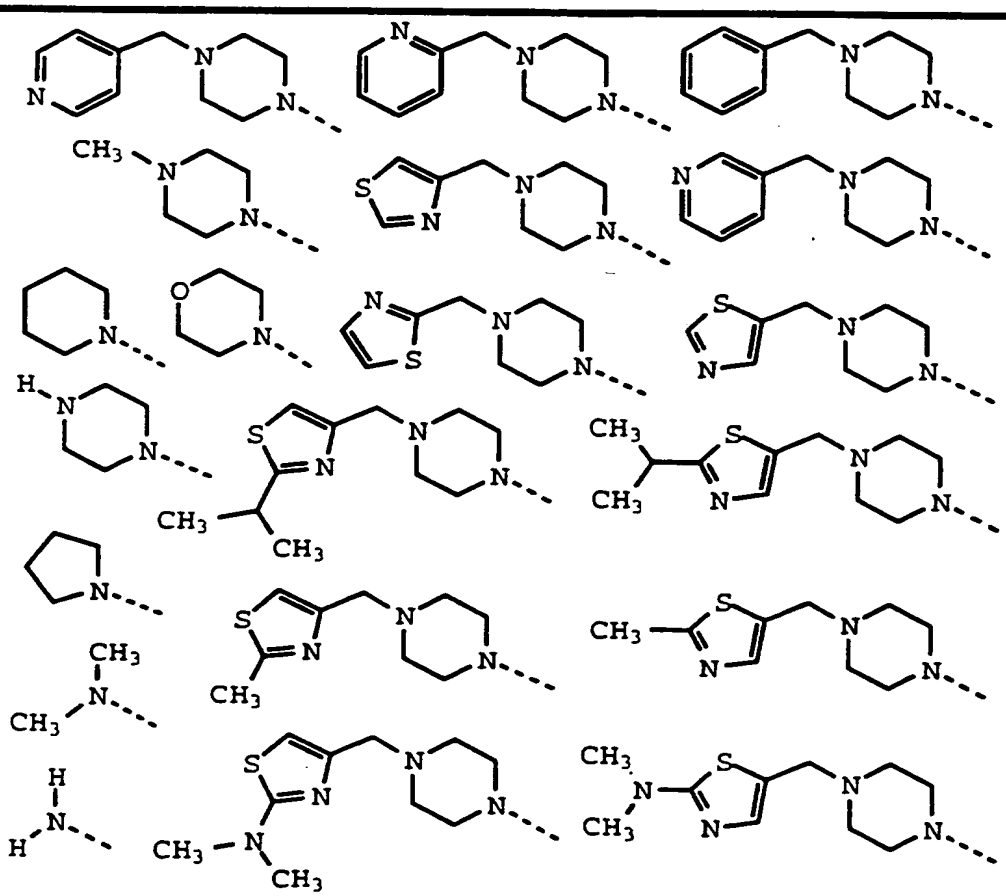
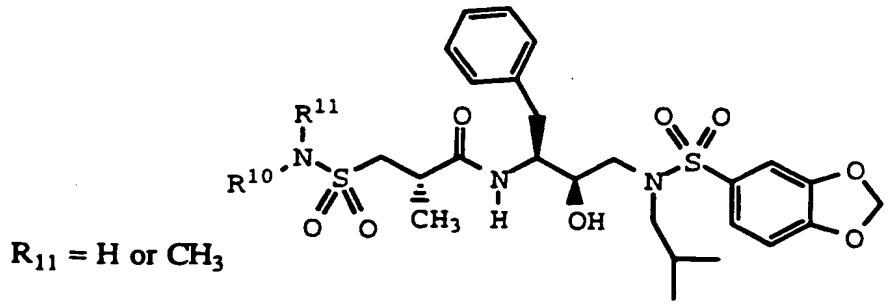


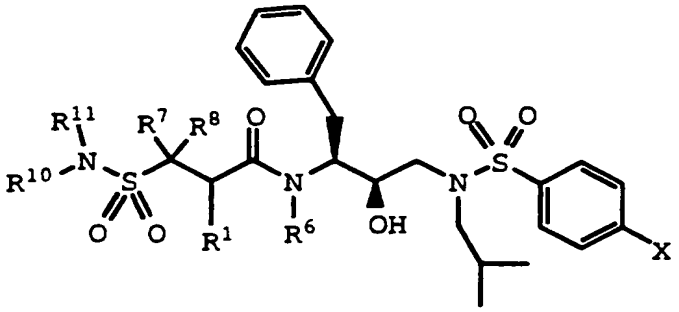
TABLE 11



R_{11} = H or CH_3

R^{10}
HO
CH_3O
CH_3, N, CH_3
N
N
O, N
CH_3, N, N
H, N, N
N
N
S, N
N, S
S, N
CH_3, N, CH_3, S, N
CH_3, S, N
CH_3, CH_3, S, N
CH_3, CH_3, S, N
CH_3, N, CH_3, S, N
CH_3, S, N

TABLE 13



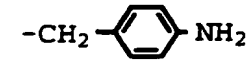
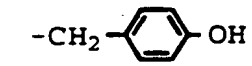
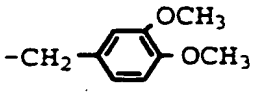
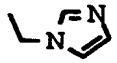
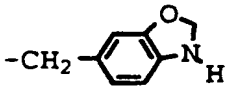
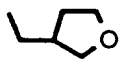
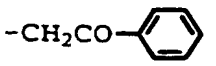
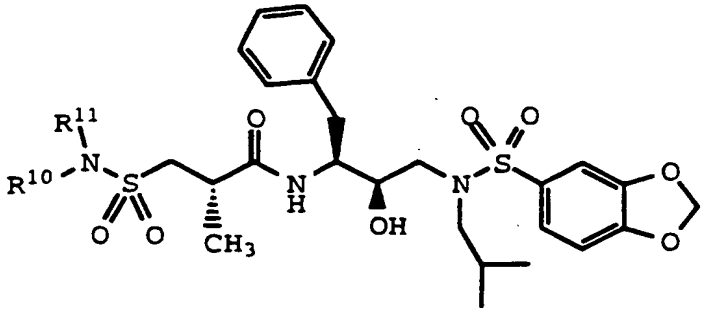
X	R^1	R^6	R^7	R^8	R^{10}	R^{11}
$-OCH_3$	$-CH_3$	-H	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$
$-OCH_3$	$-CH_3$	-H	$-CH_3$	$-CH_3$	-H	-H
$-OCH_3$	-H	-H	$-CH_3$	$-CH_3$	$-CH_3$	-H
$-NH_2$	$-CH_3$	-H	-H	-H	$-CH_3$	-benzyl
$-OCH_3$	$-CH_3$	-H	-benzyl	-H	-H	-H
$-NH_2$	$-CH_3$	-H	-H	-H	$-CH_2CH_3$	$-CH_2CH_3$
-OH	$-CH_3$	-H	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$
-H	-benzyl	-H	-H	$-CH_3$	-H	
$-OCH_3$	$-CH_3$	-H	-H	-H	-H	
$-OCH_3$	$-CH_3$	-H	-H	-H	-H	
$-OCH_3$	$-CH_3$	-H	-H	-H	-H	
$-OCH_3$	$-CH_3$	$-CH_3$	-H	-H	-H	
$-OCH_3$	$-CH_3$	-H	-H	-H	$-CH_3$	
$-OCH_3$	$-CH_3$	$-CH_3$	-H	-H	$-CH_3$	$-CH_3$
$-OCH_3$	$-CH_3$	-H	-H	-H	$-CH_3$	
$-OCH_3$	$-CH_3$	-H	-H	-H	$-CH_3$	-phenyl
$-C(NH)NH_2$	$-CH_3$	-H	-H	-H	$-CH_3$	$-CH_3$
$-C(NH)NH_2$	$-CH_3$	-H	-H	-H	$-CH_3$	-phenyl
$-C(NH)NH_2$	$-CH_3$	-H	-H	-H	$-CH_3$	-benzyl

TABLE 15



R^{10}	R^{11}
-CH_2-C(NH)NH_2	-H
-CH_2-C(NH)NH_2	-CH_3
-CH_2-C(NH)NH_2	-benzyl
C(NH)NH_2	-H
C(NH)NH_2	-CH_3
C(NH)NH_2	-benzyl
N, C(NH)NH_2	-H
N, C(NH)NH_2	-CH_3
N, C(NH)NH_2	-benzyl

$-NR^{10}R^{11}$ = N, C(NH)NH_2

$-NR^{10}R^{11}$ = N, C(NCH_3)NH_2

$-NR^{10}R^{11}$ = N, C(NH)NH_2

$-NR^{10}R^{11}$ = N, C(NCH_3)NH_2

is carried out in duplicate wells.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

Example 54

The effectiveness of various compounds were determined in the above-described enzyme assay and in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, J. Virol. Methods, 20, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a CD4+ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2µg/ml). An 80 µl volume of medium containing 1 x 10^4 cells was dispensed into each well of the tissue culture plate. To each well was added a 100µl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5 x 10^4 $TCID_{50}$ per ml ($TCID_{50}$ = the dose of virus that infects 50% of cells in tissue culture), and a 20µL volume of the virus sample (containing 1000 $TCID_{50}$ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing

infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy. The results of selected compounds are shown in Table 16.

TABLE 16

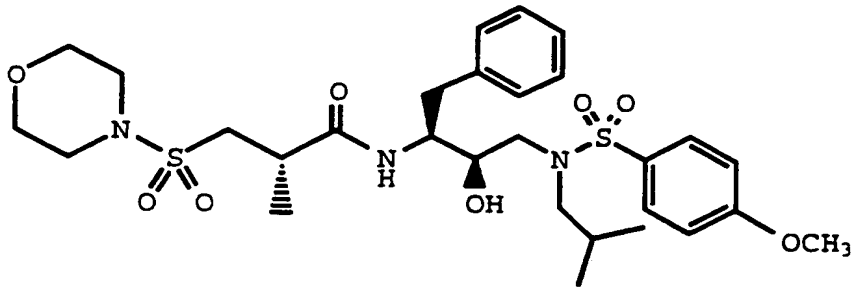
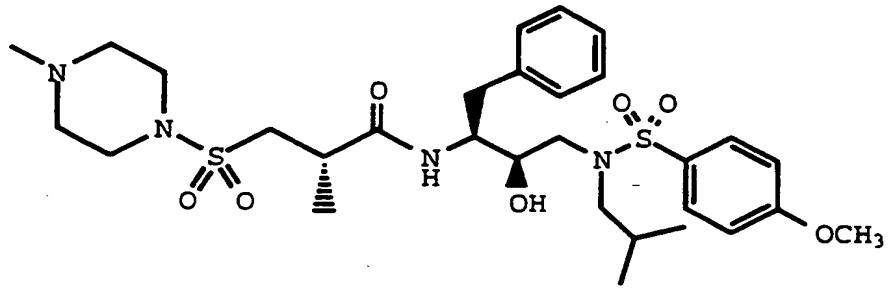
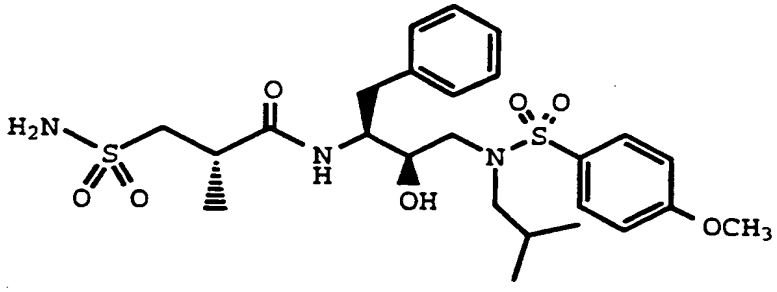
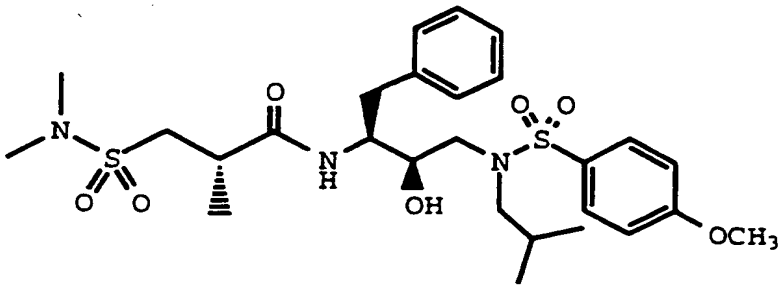
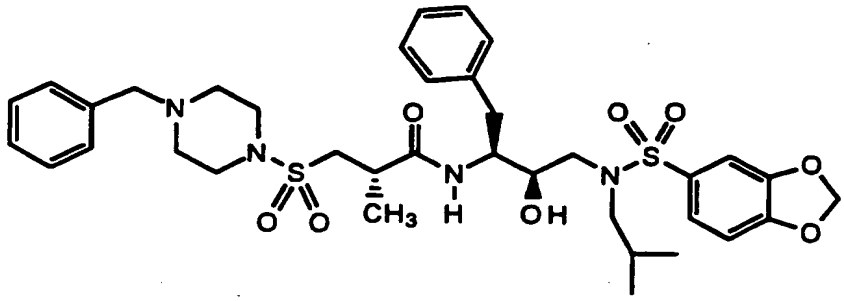
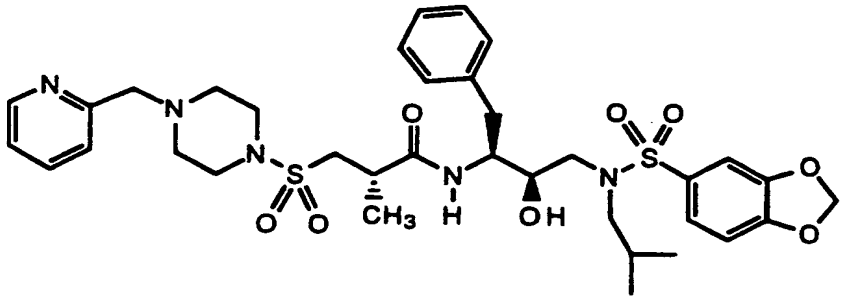
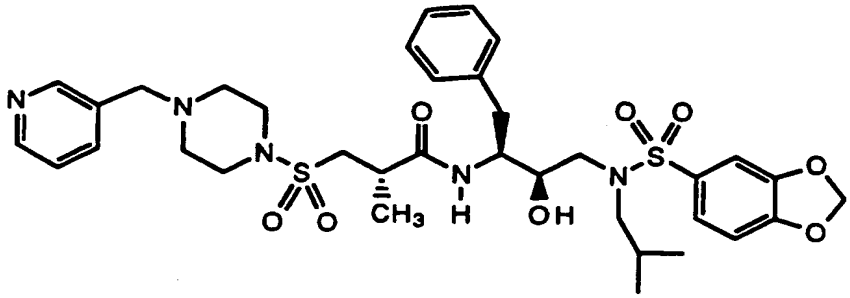
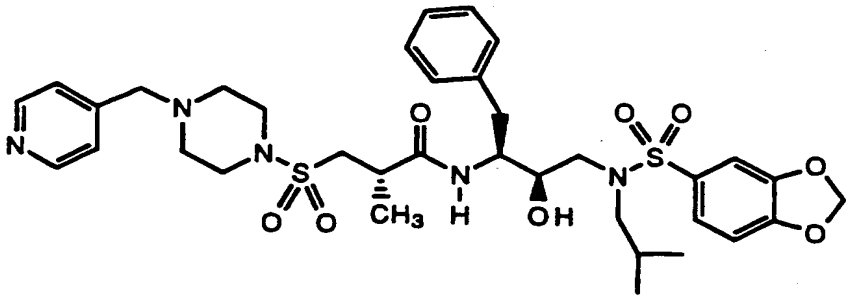
Entry	Compound	IC_{50} (nM)	EC_{50} (nM)
1		10	32
2		8	77
3		6	40
4		4	15

TABLE 16 (Cont'd)

Entry	Compound	IC_{50} (nM)	EC_{50} (nM)
9		6	84
10		10	56
11		9	
12		9	42

the subject compounds are effective in the treatment and/or proplylaxis of retroviral infections.

The subject compounds are also effective in preventing the growth of retroviruses in a solution. Both human and animal cell cultures, such as T-lymphocyte cultures, are utilized for a variety of well known purposes, such as research and diagnostic procedures including calibrators and controls. Prior to and during the growth and storage of a cell culture, the subject compounds may be added to the cell culture medium at an effective concentration to prevent the unexpected or undesired replication of a retrovirus that may inadvertently or unknowingly be present in the cell culture. The virus may be present originally in the cell culture, for example HIV is known to be present in human T-lymphocytes long before it is detectable in blood, or through exposure to the virus. This use of the subject compounds prevents the unknowing or inadvertent exposure of a potentially lethal retrovirus to a researcher or clinician.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the

pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

The compounds of the present invention can also be used in the form of prodrugs and esters of Formula I. The term "prodrug" contemplated herein is a derivative of Formula I which upon administration to a subject is chemically converted by metabolic or chemical processes to yield a compound of Formula I or a salt thereof. See H. Bundgnard, "Drugs of the Future" 16:443-458 (1991); and H. Bundgnard, "Design of Prodrugs" Elsevier, Amsterdam, 1985, both incorporated herein by reference.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular

polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

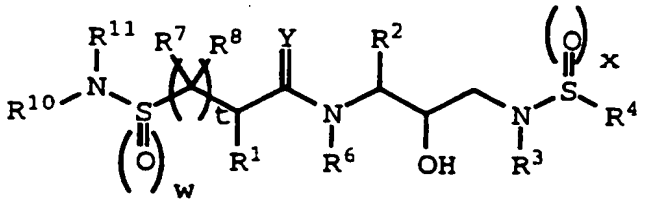
Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

WHAT IS CLAIMED IS:

1. Compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aminosulfonylalkyl, N-alkylaminosulfonylalkyl, N,N-dialkylaminosulfonylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl radicals, or an amino acid side chain of asparagine, lysine, aspartic acid, aspartic acid methyl ester, methionine or the sulfoxide (SO) or sulfone (SO_2) derivatives thereof, S-methyl cysteine or the sulfoxide (SO) or sulfone (SO_2) derivatives thereof, ornithine, leucine, isoleucine, norleucine, allo-isoleucine, alanine, phenylalanine, histidine, tert-leucine, glutamine, threonine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyano alanine or valine;

R^2 represents alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl radicals, which radicals are optionally substituted with one or more alkyl, halogen, $-NO_2$, $-CN$, $-CF_3$, $-OR^9$ or $-SR^9$ radials, wherein R^9 represents hydrogen, alkyl, aryl or heteroaryl radicals;

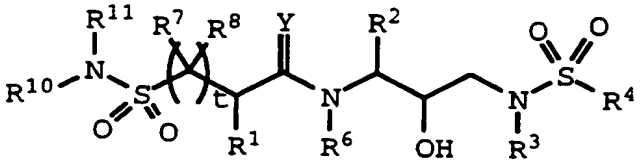
heteroaralkyl, heteroarylcarbonylalkyl, arylcarbonylalkyl, thioalkyl, alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide derivatives thereof, aminoalkyl or mono- or di-N-substituted aminoalkyl radicals, wherein said substituents are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocyclo or heterocycloalkyl radicals; or R^{10} and R^{11} together with the nitrogen to which they are attached represent heterocyclo, heteroaryl, aralkylheteroaryl, aralkylheterocyclo, heteroaralkylheteroaryl or heteroaralkylheterocyclo radicals;

x and w each represent 0, 1 or 2;

t represents 0-6; and

Y represents O, S or NH.

2. The compound of Claim 1 represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R^1 represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)2(SCH_3)$, $-C(CH_3)2(S[O]CH_3)$, $-C(CH_3)2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aminosulfonylalkyl, N-alkylaminosulfonylalkyl, N,N-dialkylaminosulfonylalkyl or heteroaralkyl radicals, or an amino acid side chain of asparagine, lysine, aspartic acid, aspartic acid methyl ester, methionine or the

R^6 represents hydrogen or alkyl radicals;

each R^7 independently represents hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, carboxy, amidino, N-alkylamidino, alkyl, aryl or aralkyl radicals; or R^7 together with R^1 and the carbon atoms to which R^1 and R^7 are attached, represent cycloalkyl or heterocyclo radicals;

each R^8 independently represents hydrogen or alkyl radicals;

R^{10} represents hydrogen, alkyl, aryl, aralkyl, heterocyclo, heterocycloalkyl, heteroaryl or heteroaralkyl radicals;

R^{11} represents hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroarylcarbonylalkyl, arylcarbonylalkyl, thioalkyl, alkylthioalkyl or arylthioalkyl radicals or the corresponding sulfone or sulfoxide derivatives thereof, aminoalkyl or mono- or di-N-substituted aminoalkyl radicals, wherein said substituents are alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocyclo or heterocycloalkyl radicals; or R^{10} and R^{11} together with the nitrogen to which they are attached represent heterocyclo, heteroaryl, aralkylheteroaryl, aralkylheterocyclo, heteroaralkylheteroaryl or heteroaralkylheterocyclo radicals;

t represents 0-4; and

Y represents O, S or NH.

R^6 represents hydrogen or alkyl radicals;

each R^7 independently represents hydrogen, $-CO_2CH_3$, $-CONH_2$, carboxy, amidino, N-alkylamidino, alkyl, aryl or aralkyl radicals; or R^7 together with R^1 and the carbon atoms to which R^1 and R^7 are attached, represent cycloalkyl or heterocyclo radicals;

each R^8 independently represents hydrogen or alkyl radicals;

R^{10} represents hydrogen, alkyl, aralkyl or heteroaralkyl radicals;

R^{11} represents hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, cycloalkyl, cycloalkylalkyl, heterocyclo, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heteroarylcarbonylalkyl or arylcarbonylalkyl radicals; or R^{10} and R^{11} together with the nitrogen to which they are attached represent heterocyclo, heteroaryl, aralkylheteroaryl, aralkylheterocyclo, heteroaralkylheteroaryl or heteroaralkylheterocyclo radicals;

t represents 0-4; and

Y represents O or S.

4. The compound of Claim 3 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R^1 represents hydrogen, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aminosulfonylalkyl, N-alkylaminosulfonylalkyl, N,N-dialkylaminosulfonylalkyl or heteroaralkyl radicals, or

R^{11} represents hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, N,N-dialkylaminoalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl or arylcarbonylalkyl radicals; or R^{10} and R^{11} together with the nitrogen to which they are attached represent heterocyclo, heteroaryl, heteroaralkylheteroaryl or heteroaralkylheterocyclo radicals;

t represents 0-2; and

Y represents O or S.

5. The compound of Claim 4 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R^1 represents hydrogen, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, $-CF_3$, methyl, ethyl, isopropyl, iso-butyl, sec-butyl, tert-butyl, propenyl, propargyl, aminosulfonylmethyl, N,N-dimethylaminosulfonylmethyl, aminosulfonylethyl, N,N-dimethylaminosulfonylethyl, thiazolylmethyl, cyclohexyl or cyclohexylmethyl radicals, or an amino acid side chain of asparagine, lysine, aspartic acid, aspartic acid methyl ester, methionine or the sulfoxide (SO) or sulfone (SO_2) derivatives thereof, S-methyl cysteine or the sulfoxide (SO) or sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, phenylalanine, histidine, tert-leucine or valine;

R^2 represents $CH_3SCH_2CH_2$-, iso-butyl, n-butyl, benzyl, fluorobenzyl, hydroxybenzyl, methoxybenzyl, thiazolylmethyl, phenylthiomethyl, naphthylthiomethyl, naphthylmethyl or cyclohexylmethyl radicals;

R^3 represents methyl, isoamyl, iso-butyl, n-butyl, propyl, 2-methylbutyl, propenyl, propargyl, hydroxybutyl,

R^{11} represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, hydroxyethyl, methoxyethyl, N,N-dimethylaminoethyl, cyclohexylmethyl, phenyl, amidinophenyl, pyridyl, amidinopyridyl, benzyl, hydroxybenzyl, methoxybenzyl, dimethoxybenzyl, aminobenzyl, amidinobenzyl, phenylcarbonylmethyl, diphenylmethyl, pyridylmethyl, imidazolylmethyl, (2,3-dihydrobenzoxazolyl)methyl, tetrahydrofuranylmethyl, pyrrolidinylethyl, piperidinylethyl, morpholinylethyl, piperazinylethyl, N-methylpiperazinylethyl, N-benzylpiperazinylethyl, (N-methylaminothiazolyl)methyl, (N,N-dimethylaminothiazolyl)methyl, thiazolylmethyl or (isopropylthiazolyl)methyl radicals; or R^{10} and R^{11} together with the nitrogen to which they are attached represent piperidinyl, morpholinyl, piperazinyl, N-methylpiperazinyl, pyrrolidinyl, amidinopyrrolidinyl, (N-methylamidino)pyrrolidinyl, pyrrolyl, amidinopyrrolyl, (N-methylamidino)pyrrolyl, N-benzylpiperazinyl, N-(pyridylmethyl)piperazinyl, N-[(N-methylaminothiazolyl)methyl]piperazinyl, N-[(N,N-dimethylaminothiazolyl)methyl]piperazinyl, N-(thiazolylmethyl)piperazinyl or N-[(isopropylthiazolyl)methyl]piperazinyl radicals;

t represents 0 or 1; and

Y represents O.

6. The compound of Claim 5 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R^1 represents hydrogen, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, $-CF_3$, methyl, ethyl, isopropyl, propyl, tert-butyl, aminosulfonylmethyl or N,N-dimethylaminosulfonylmethyl radicals, or an amino acid side chain of asparagine, isoleucine, allo-isoleucine, alanine, tert-leucine or valine;

benzylpiperazinyl, N-(pyridylmethyl)piperazinyl or N-(thiazolylmethyl)piperazinyl radicals;

t represents 0 or 1; and

Y represents O.

7. The compound of Claim 3 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R^1 represents hydrogen or alkyl radicals, or an amino acid side chain of leucine, norleucine, isoleucine, allo-isoleucine, alanine, tert-leucine or valine;

R^2 represents cycloalkylalkyl or aralkyl radicals, which radicals are optionally substituted with one or more halogen, $-OR^9$ or $-SR^9$ radials, wherein R^9 represents aryl radicals;

R^3 represents alkyl, cycloalkyl or cycloalkylalkyl radicals;

R^4 represents heterocyclo, heteroaryl or aryl radicals, which radicals are optionally substituted with one or more alkyl, alkoxy, alkylthio, halo, amino or alkoxycarbonylamino radical;

R^6 represents hydrogen radical;

each R^7 independently represents hydrogen or alkyl radicals;

each R^8 independently represents hydrogen or alkyl radicals;

R^{10} represents hydrogen, alkyl or aralkyl radicals;

each R^8 independently represents hydrogen or methyl radicals;

R^{10} represents hydrogen, methyl, ethyl or benzyl radicals;

R^{11} represents hydrogen, methyl, N,N-dimethylaminoethyl, benzyl, pyridylmethyl, pyrrolidinylethyl, piperidinylethyl, morpholinylethyl, piperazinylethyl or thiazolylmethyl radicals; or R^{10} and R^{11} together with the nitrogen to which they are attached represent piperidinyl, morpholinyl, piperazinyl, N-methylpiperazinyl, pyrrolidinyl, pyrrolyl, N-benzylpiperazinyl, N-(pyridylmethyl)piperazinyl or N-(thiazolylmethyl)piperazinyl radicals;

t represents 1; and

Y represents O.

9. The compound of Claim 1 which is:

N^1-[1-[N-(2-methylpropyl)-N-(phenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-(1-morpholinosulfonyl)-2(R)-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-(phenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[(4-methylpiperizin-1-yl)sulfonyl]-2(R)-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-(phenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-aminosulfonyl-2(R)-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-(phenylsulfonyl)amino]-2R-hydroxy-3(S)-(phenylmethyl)prop-3-yl]-3-[(dimethylamino)sulfonyl]-2(R)-methylpropionamide;

[[4-(3-pyridylmethyl)piperazin-1-yl]sulfonyl]-2R-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-[(1,3-benzodioxol-5-yl) sulfonyl]amino]-2R-hydroxy-3S-(phenylmethyl)prop-3-yl]-3-[[4-(2-pyridylmethyl)piperazin-1-yl]sulfonyl]-2R-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-[(1,3-benzodioxol-5-yl) sulfonyl]amino]-2R-hydroxy-3S-(phenylmethyl)prop-3-yl]-3-[[4-(2-pyridylmethyl)piperazin-1-yl]sulfonyl]-2R-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-[(1,3-benzodioxol-5-yl) sulfonyl]amino]-2R-hydroxy-3S-(phenylmethyl)prop-3-yl]-3-[(dimethylamino)sulfonyl]-2R-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-[(1,3-benzodioxol-5-yl) sulfonyl]amino]-2R-hydroxy-3S-(phenylmethyl)prop-3-yl]-3-[(1-morpholinyl)sulfonyl]-2R-methylpropionamide;

N^1-[1-[N-(2-methylpropyl)-N-[(1,3-benzodioxol-5-yl) sulfonyl]amino]-2R-hydroxy-3S-(phenylmethyl)prop-3-yl]-3-[(1-pyrrolidinyl)sulfonyl]-2R-methylpropionamide; or

N^1-[1-[N-(2-methylpropyl)-N-[(1,3-benzodioxol-5-yl) sulfonyl]amino]-2R-hydroxy-3S-(phenylmethyl)prop-3-yl]-3-[(1-piperidinyl)sulfonyl]-2R-methylpropionamide.

10. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

11. Method of inhibiting a retroviral protease comprising administering an effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

Inter onal application No.
PCT/US 96/00607

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 11-16 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The terms "prodrug" and "ester" are imprecise and it is not possible to determine which compounds are meant by them. Since there are no examples of prodrugs or esters of compounds of Claim 1 in the description, they were not included in the search. (Claims searched incompl. 9)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment f additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio Application No
PCT/US 96/00607

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